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For the Study of the CIRCULATION

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Contents on Inside Cover

American Heart Journal

CONTENTS FOR MAY, 1948

Original Communications

Studies on the Coronary Circulation. III. Collateral Circulation of Beating Human and Dog Hearts With Coronary Occlusion. Myron Prinzmetal, M.D., H. C. Bergman, Ph.D., H. E. Kruger, Lois L. Schwartz, M.D., Benjamin Simkin, M.D., and Sidney S. Sobin, M.D., Los Angeles, Calif. 689

The Diagnosis of Mitral Insufficiency in Rheumatic Children. Ann G. Kuttner, M.D., and Milton Markowitz, M.D., Irvington-on-Hudson, N. Y. 718

The Relation of Unipolar Limb Leads to Precordial and Esophageal Leads. Gordon B. Myers, M.D., and Howard A. Klein, M.D., Detroit, Mich. 727

A New Electronic Method for Simultaneous Recording of the Ballistocardiograph and Electrocardiograph. Herbert R. Brown, Jr., M.D., and Raymond Pearson, M.D., Rochester, N. Y. 756

Seasonal Variations in Heart and Coronary Disease as Related to Various Environmental Factors. Herbert R. Brown, Jr., M.D., and Raymond Pearson, M.D., Rochester, N. Y. 763

A Note on the Importance of Proper Technique in the Recording of the Precordial Electrocardiogram. Robert F. Ziegler, M.D., Baltimore, Md. 769

Observations on the Effects on the Lungs of Respiratory Air Flow Resistance in Dogs With Special Reference to Vagotomy. S. Zinberg, M.D., G. Nudell, M.D., W. G. Kubicek, Ph.D., and M. B. Visscher, M.D., Minneapolis, Minn. 774

Measurement of the Total Transverse Diameter of the Heart by Direct Percussion. William D. Stroud, M.D., Morris W. Stroud, III, M.D., and David S. Marshall, M.D., Philadelphia, Pa. 780

Intensity and Duration of Action of Quinidine Sulfate in Auricular Fibrillation and Flutter. René Wégria, M.D., New York, N. Y. 787

Experiences With a New Synthetic Analgesic, Amidone: Its Action on Ischemic Pains of Occlusive Arterial Diseases. Roy J. Popkin, M.D., Los Angeles, Calif. 793

Electrocardiographic Changes in Pulmonary Collapse Therapy. I. Artificial Pneumothorax. D. Feldman, M.D., and C. Silverberg, M.D., St. Louis, Mo. 800

Clinical Reports

Neoplastic Involvement of Pericardium Producing the Syndrome of Constrictive Pericarditis. J. W. Fischer, M.D., Chicago, Ill. 813

Congenital Pulmonary Stenosis. Mason I. Lowance, M.D., Eugenia C. Jones, M.D., Warren B. Matthews, M.D., and Edgar M. Dunstan, M.D., Atlanta, Ga. 820

Abstracts and Reviews

Selected Abstracts 825

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American Heart Journal

VOL. 35 MAY, 1948 NO. 5

Original Communications

STUDIES ON THE CORONARY CIRCULATION. III. COLLATERAL CIRCULATION OF BEATING HUMAN AND DOG HEARTS WITH CORONARY OCCLUSION

MYRON PRINZMETAL, M.D., H. C. BERGMAN, Ph.D., H. E. KRUGER, LOIS L. SCHWARTZ, M.D., BENJAMIN SIMKIN, M.D., AND SIDNEY S. SOBIN, M.D.
LOS ANGELES, CALIF.

INTRODUCTION

ALTHOUGH much study has been devoted to the collateral circulation of the heart, much still remains to be learned, especially with regard to the functional role of this circulation immediately following acute coronary occlusion during life. Recent investigations conducted in this laboratory[1,2] provide further evidence that various types of anastomotic channels exist in the normal human heart after death and that these communications comprise the basis of a potentially extensive collateral circulation. This work was essentially anatomic in nature and did not elucidate the physiologic significance of the various anastomotic vessels. In spite of the anatomic demonstration of coronary anastomotic channels, the prevailing view still is that these channels have no functional significance and that the normal coronary arteries are end arteries.[3-7]

In order to gain further insight regarding the functional role of the collateral circulation in the normal heart, a series of brief experiments was performed in which the collateral circulation was studied during life immediately after acute experimental coronary occlusion in previously normal hearts, with special reference to the following considerations: (1) the effectiveness and extent of the

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The authors wish to extend their thanks to Dr. Irving Krakower, Edward M. Ornitz, Jr., and H. G. Liberty, Jr., for aid in the conduction of this study.

anastomotic circulation immediately after acute coronary occlusion during life; (2) a correlation of the present experimental findings with known pathologic observations concerning the size, shape, and location of myocardial infarcts; (3) an evaluation of the functions performed by the collateral circulation immediately after acute coronary closure; and (4) the relative contribution of the Thebesian-luminal group of vessels and the intercoronary anastomoses to the blood supply of myocardium rendered ischemic by ligation of the anterior descending branch of the left coronary artery in the dog.

PART I. THE IN-VIVO DISTRIBUTION OF RADIOACTIVE ERYTHROCYTES IN THE NORMAL AND INFARCTED HUMAN HEART

Since the prime purpose of our investigations on the collateral circulation is a better understanding of the functional significance of this circulation after coronary occlusion in man during life, an attempt was made to study the collateral circulation in patients with recent coronary occlusions by the use of labelled erythrocytes as tracer constituents of circulating blood. Human erythrocytes labelled with radioactive phosphorus were employed for this purpose because of the high degree of sensitivity with which these cells could be measured; as little as 0.001 c.c. of blood could be accurately determined. Human radioactive erythrocytes were injected into moribund patients shortly before death. In those patients who came to autopsy, the heart was removed and the distribution of the radioactive red cells was quantitatively determined by the Geiger counter and radioautographs. In hearts with myocardial infarction, the radioactivity in the region of infarction was compared with the radioactivity in the uninvolved contiguous myocardium.

Although the experiments on man reported in this section were not entirely satisfactory, for reasons to be discussed, it is believed that they are worth reporting because (1) they have fundamental significance, and (2) they point the way for the experiments on dogs which comprise the rest of this paper.

Details of Procedure.—Human, Type O, sterile erythrocytes were labelled with radioactive phosphorus* (P_{32} in the form of Na_2HPO_4), as described in a previous communication.[2] The radiophosphorus used in tagging the erythrocytes was autoclaved at 15 pounds pressure for twenty minutes, and equilibration and washing of the red blood cells was carried out in a sterile manner. A 25 c.c. volume of radioactive cells was stored in the cold, and just prior to injection an equal volume of sterile normal saline was added. The final radioactive erythrocyte-saline suspension contained 0.2 to 1.0 millicurie of P_{32}: this amount of radiation is small and has been found to be innocuous in man.

The radioactive erythrocyte-saline suspension was slowly injected intravenously into moribund patients. At autopsy, a sample of blood was obtained from a ventricular cavity and the heart was removed and opened by the Schlesinger method.[3] The distribution of the labelled red cells in the ventricular

*The radioactive phosphorus was obtained from Monsanto Chemical Company, Clinton Laboratories, Box W, Knoxville, Tenn.

myocardium was determined quantitatively with a Geiger counter at specific areas on the endocardial and pericardial surfaces and by radioautographs of these surfaces. The amount of blood contained in each gram of heart muscle was calculated on the basis of the radioactivity (Geiger counter) measured in 0.01 c.c. of heart's blood obtained at autopsy.* Radioautographs were obtained by exposing the heart, which had been fixed in formalin, to x-ray film for several days. The resulting shadows on the exposed plate were produced by beta ray irradiation from the radiophosphorus in the erythrocytes. The intensity of the shadow was proportional to the amount of blood in various regions and was found to correlate fairly well with the results obtained by the Geiger counter in corresponding areas. Further details of these procedures have been reported previously.[2] In addition, a radiopaque mixture[2] was injected into the right and left coronary arteries so that the outlines of the major coronary arteries could be determined by routine x-ray. The course of these arteries was superimposed upon the radioautograph for orientation.

With the techniques described, two normal hearts and three hearts from patients with myocardial infarction who came to autopsy four days, twelve days, and eight weeks, respectively, after the onset of their attacks were studied.

Results. —In the two normal hearts the radioactive red cells were distributed equally throughout the ventricular myocardium. No marked difference was noted in the findings on the pericardial and endocardial surfaces. A radioautograph of one of the normal hearts is shown in Fig. 1. The diffuse dark gray background is from the myocardium proper, due to beta ray irradiation from capillary blood and probably also from radiophosphorus that has diffused out of the erythrocytes. The large dark vessels are probably veins, since the arteries are generally constricted and empty at death.

There were similar findings in the three hearts with myocardial infarction, and significantly, the same volume of blood per gram of tissue was contained in the infarcted myocardium as in the uninvolved contiguous heart muscles. This was true on both the endocardial and pericardial surfaces. This is illustrated in an autoradiograph of the heart of a patient with an infarct eight weeks old (Fig. 2). Fig. 3 illustrates an x-ray of the same heart with the coronary arteries injected with a radiopaque mass demonstrating the vascular lesions and the extensive collateral circulation to the infarcted tissue. These observations would apparently indicate that an active and functioning collateral circulation was responsible for the passage of blood into infarcted heart muscle during life.

Discussion.—These experiments may bear two criticisms. First, because of the long period (hours or days) elapsing between the injection of the radioactive erythrocytes and the death of the patient, there was a good possibility

---

*Method of calculation:

$$\text{cubic centimeters of blood per gram tissue} = \text{factor} \times \left(\frac{\text{counts per minute per surface area tissue}}{\text{counts per minute per 1 c.c. blood}} \right)$$

Factor for conversion of counts per cm.² tissue to counts per gram tissue = 2.1.

This factor is based on the tissue absorption of the beta rays emitted by P_{32}. We are grateful to Dr. Hardin Jones for the calculation of this factor.

Surface area of tissue measured in these experiments was 2.1 centimeters².

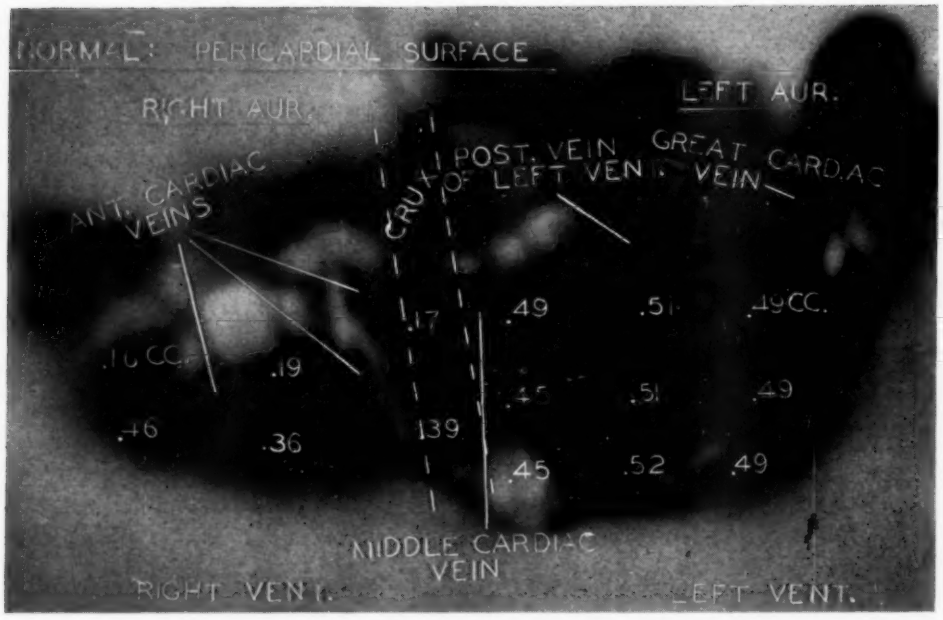


Fig. 1.—Radioautograph. A 28-year-old woman who died of cirrhosis of the liver. Normal heart. Fifty milliliters of radioactive erythrocytes injected intravenously six days before death. Heart was unrolled so that all of the coronary arteries lay in one plane. Pericardial surface exposed to x-ray film for ten days. The suerpimposed numbers represent volume of blood in cubic centimeters per gram of heart muscle as determined by surface Geiger count measurements. The outlines of the vessels can be seen. This normal heart is shown so that the pathologic human hearts can be compared. The veins are well outlined.

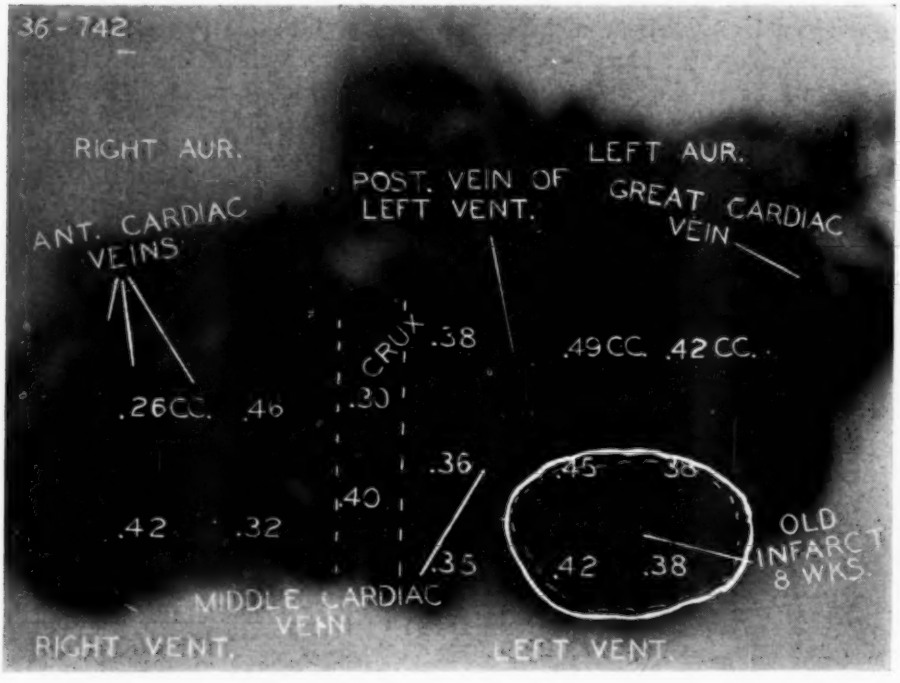


Fig. 2.—Radioautograph. A 38-year-old woman who died of uremia due to intercapillary glomerulosclerosis. Arteriosclerotic heart disease with 8-week-old myocardial infarction. Ninety-five cubic centimeters of radioactive red cells injected intravenously thirty-seven hours before death. Pericardial surface exposed to x-ray film for ninety-six hours. The vascular capacity of the 8-week-old infarct is the same as the surrounding myocardium.

that much of the radiophosphorus was released from the red cells into the plasma as free phosphorus. If this occurred, free radiophosphorus may have diffused through the heart and the measurements of radioactivity per gram of tissue may not have been indicative, accurately, of labelled erythrocytes. This is especially true since it has been found that heart muscle takes up a significant amount of free radiophosphorus injected into the blood stream.[9] Calculated amounts of blood per gram of tissue, therefore, are by no means accurate because it was not

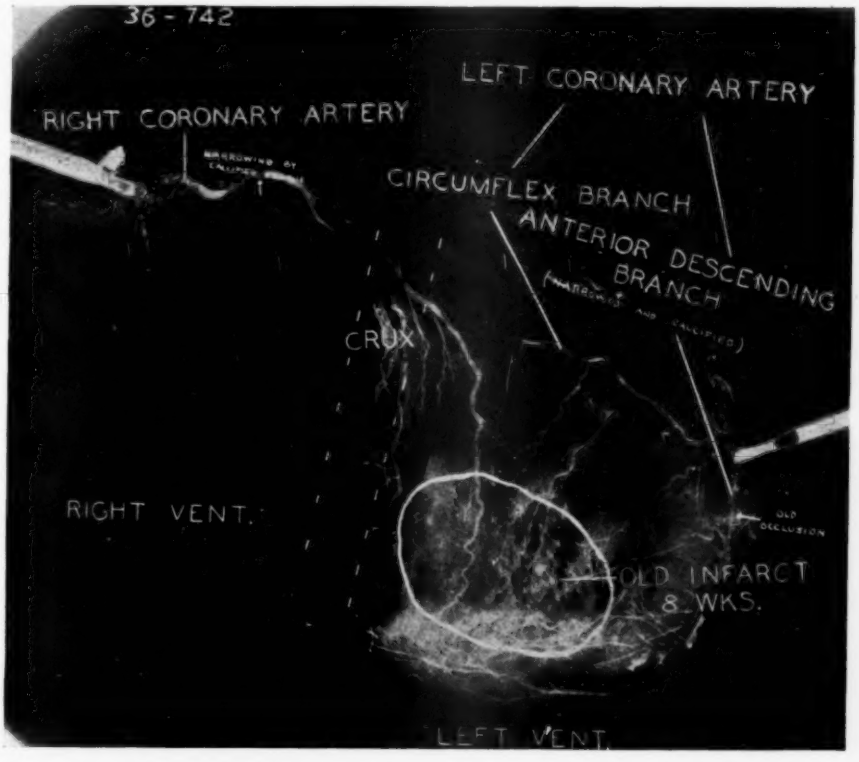


Fig. 3.—X-ray of heart injected with radiopaque mass. Same heart as shown in Fig. 2. Radiopaque mass injected into right and left coronary arteries so that major vessels are outlined. The pathologic findings, as determined by dissection, are indicated. The left anterior descending artery was narrowed and calcified throughout its length, and there was an old occlusion 2 cm. from its origin. In the right coronary artery there was an area of extreme narrowing with calcification 4 cm. distal to the ostium. The site of the infarct is outlined. The abundant collateral vessels to the infarcted area at eight weeks are shown.

known how much free phosphorus was released from the red cells. Despite this, the findings are still fundamentally significant because even free radiophosphorus could not have entered the center of a region of myocardial infarction unless brought in through collateral channels. A second objection to this type of experiment is the occurrence of various types of terminal states in each of these patients, including shock, with its attendant hemodynamic changes. For example, there is known to be an increased volume of blood in the myocardium in experimental

shock.[10] It is quite probable that such hemodynamic alterations occurred terminally in these patients. *Despite such criticisms, these experiments demonstrate that in the arteriosclerotic heart with myocardial infarction in living man there is a functioning collateral circulation that allows blood to enter all parts of a myocardial infarction, including the central portions.*

PART II. ACUTE CORONARY OCCLUSION IN THE DOG; THE EXISTENCE OF FUNCTIONAL COLLATERAL CIRCULATION IN THE HEART WITH OCCLUSION OF THE ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY

Because of the uncontrollable factors inherent in the experimental procedure for man, as described in Part I, experiments of a similar nature were performed on dogs wherein the experimental conditions could be properly controlled, and more reliable information obtained about the coronary circulation immediately following acute arterial occlusion.

Method.—In the period immediately after ligation of the anterior descending artery in the dog, the collateral circulation to the resulting *ischemic* or *potentially infarcted* myocardium was studied by the radioactive-erythrocyte technique. To prevent cardiac hemodynamic alterations that occur with various modes of death,[11] the heart was stopped abruptly with a freezing mixture.

Details of the Procedure.—Fourteen dogs were anesthetized with sodium pentobarbital and maintained with artificial respiration. Through an incision in the anterior chest wall to the left of the sternum, the left fourth and fifth costal cartilages were resected. The left pleural cavity and the mediastinum were opened. The pericardial sac was incised and the pericardial flaps were reflected and sutured to the chest wall, thus providing full exposure of the heart. The anterior descending branch of the left coronary artery was dissected free and ligated. The femoral arterial pressure was recorded by means of a mercury manometer. The site of the coronary artery ligation was approximately 2 cm. from the origin of the anterior descending branch of the left coronary artery. In order to reduce the incidence of ventricular fibrillation after coronary artery ligation, atropine, 0.1 mg. per kilogram of body weight, was given intravenously shortly before the ligation.[12]

Dog erythrocytes were labelled with radiophosphorus, as described in Part I for human blood. The cells were washed twice and resuspended in an equal volume of normal saline just before injection. Five to ten cubic centimeters of the erythrocyte-saline suspension containing 1 to 3 mc. of P_{32} were given intravenously from one and one-half to thirty minutes after ligation of the anterior descending branch. The interval between the time of injection of the radioactive red cells and the stopping of the heart by freezing varied between twenty-five seconds and ten minutes in different animals. The heart was stopped by pouring a freezing mixture of carbon dioxide snow and methyl cellosolve (at about −70°C.) over the entire heart; ventricular contraction ceased completely within two seconds or less. A sample of blood was withdrawn from the left ventricular cavity and the heart was removed and opened by the Schlesinger method.[8] As was

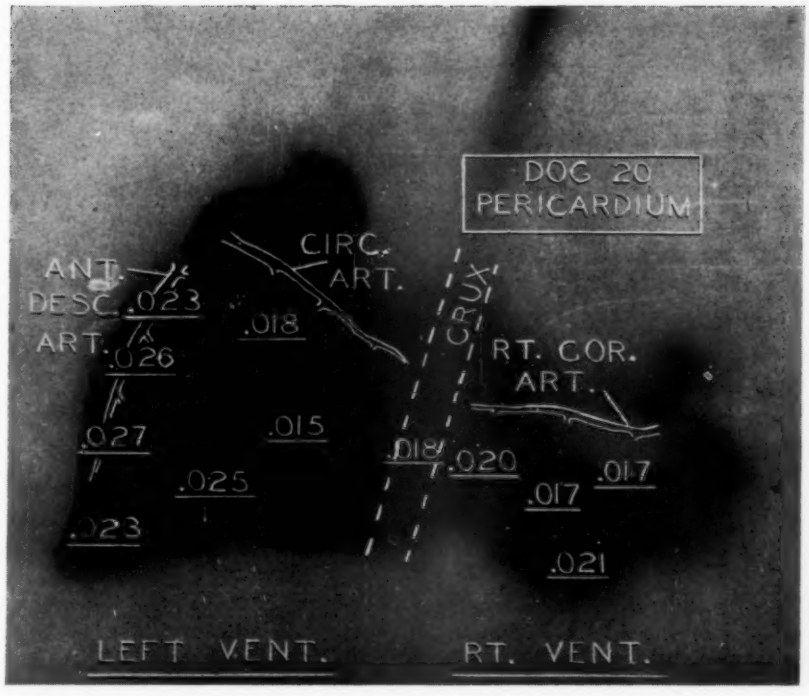


Fig. 4.—Radioautograph. Normal dog heart. Pericardial surface. Radioactive erythrocytes injected into femoral vein. Heart stopped by freezing twenty-five seconds after injection of radioactive erythrocytes. Pericardial surface exposed to x-ray film for several days. The superimposed numbers represent the volume of blood in milliliters per gram of heart muscle as determined by surface Geiger count measurements. The major coronary arteries are drawn in for purposes of orientation. The quantity of circulating blood is the same throughout the pericardial surface of the normal dog heart.

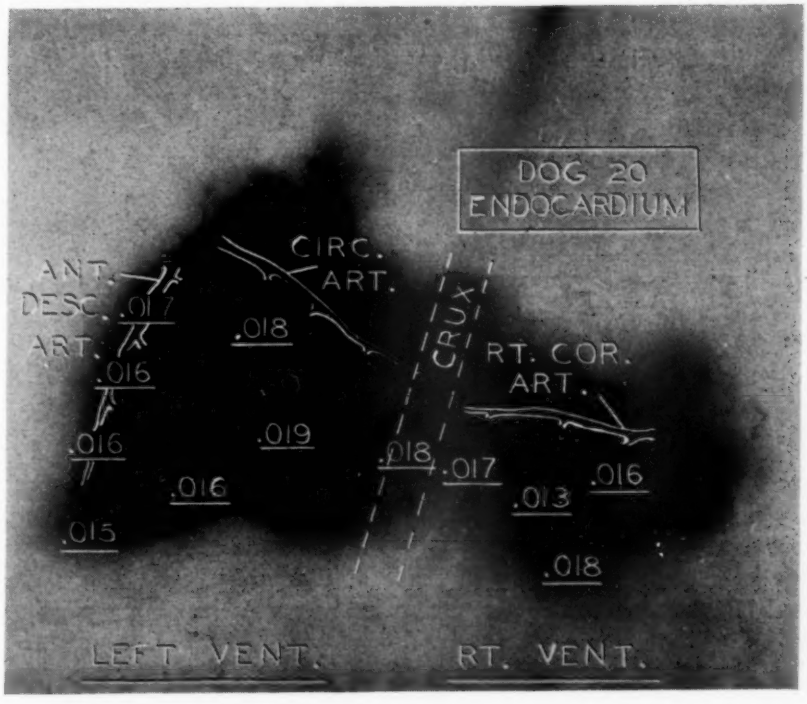


Fig. 5.—Radioautograph. Normal dog heart. Endocardial surface. Same dog heart as shown in Fig. 4. Endocardial surface exposed to x-ray film for same length of time. On this surface also the quantity of circulating blood is the same throughout.

done in Part I, the distribution and concentration of the radioactive erythrocytes in both the endocardial and the pericardial portions of the ventricular myocardium were determined by means of the Geiger counter and radioautographs. The calculations were based upon the amount of radioactivity present in 0.01 c.c. of the heart's blood.

These experiments were designed to overcome the criticism of experiments on the human heart described in Part I. First, in the short time that the red cells circulated, only minute amounts of phoshporus could diffuse from the red cells, and, therefore, the calculated volume of red blood cells is accurate. Second, the rapid method of stopping the heart by freezing overcomes the terminal hemodynamic changes which probably occur in the dying human heart.

The identical procedure was performed on two control animals without coronary ligation.

Results.—Radioactive erythrocytes were found in all parts of the normal myocardium (Figs. 4 and 5). In all experiments, radioactive erythrocytes were also found in all parts of the pericardial and endocardial portions of the ischemic myocardium distal to the point of arterial ligation, showing the existence of functional anastomotic channels supplying the ischemic myocardium during life (Figs. 6 to 10; Table I).

Extent of Collateral Circulation.—The calculated volume of blood in the pericardial portion of the ischemic myocardium, including the central portion of this ischemic region, was statistically equal to the volume of blood in the pericardial portion of the contiguous nonischemic left ventricular myocardium (Figs. 6, 8, and 10; Table I). On the endocardial side, however, there was a significant diminution in the volume of blood (approximately one-third less) in the ischemic as compared with the nonischemic myocardium of the left ventricle (Figs. 7, 9, and 10; Table I).

On the anterior aspect of the dog's right ventricle a narrow band of myocardium adjacent to the anterior longitudinal groove is also normally supplied by branches of the anterior descending branch of the left coronary artery.[13] On the pericardial side, the amount of radioactivity contained in this portion of the right ventricular myocardium was equal to the amount of radioactivity contained in the surrounding nonischemic right ventricular myocardium, as was the case in the infarcted and uninfarcted portions of the left ventricle. On the endocardial side, however, in contrast to the corresponding side of the ischemic left ventricular myocardium, the ischemic portion of the right ventricle contained as much blood as the nonischemic portion of this ventricle.

These findings allow the following conclusions: (1) Blood from collateral channels supplies the entire portion of ischemic myocardium distal to a ligated coronary artery; (2) the pericardial side of ischemic myocardium of the left ventricle is better nourished by the collateral circulation than the endocardial side; and (3) the small portion of ischemic right ventricular myocardium, normally supplied by the ligated anterior descending artery, is better nourished by collateral blood than a similar portion of the left ventricle.

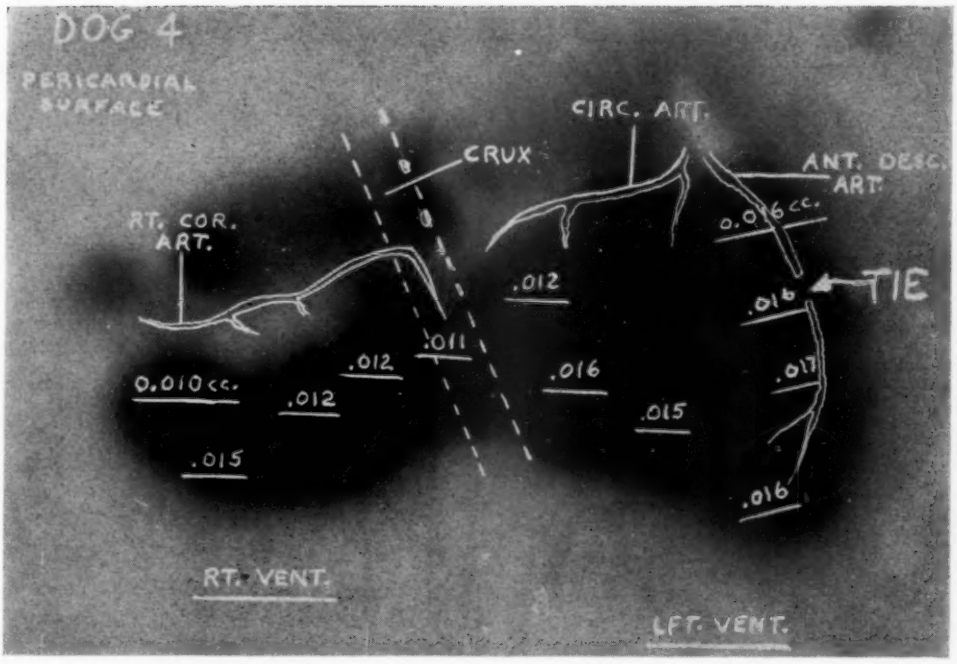


Fig. 6.—Radioautograph. Dog heart. Anterior descending branch of left coronary artery ligated. Nine milliliters of radioactive erythrocytes injected into femoral vein seven minutes later. Heart stopped by pouring carbon dioxide snow over it five minutes after radioactive cells injected. Pericardial surface exposed to x-ray film for thirteen days. It can be seen that the quantity of circulating blood is the same in the ischemic area distal to the tie as in the surrounding normal nonischemic myocardium.

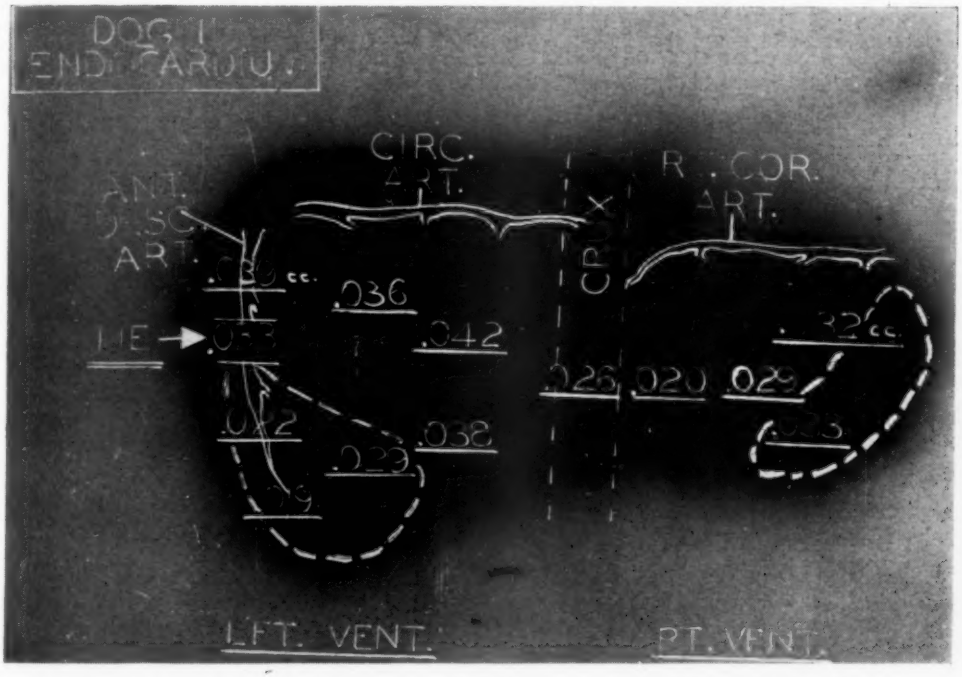


Fig. 7.—Radioautograph. Dog heart. Anterior descending branch of left coronary artery ligated. Five milliliters of radioactive erythrocytes injected into femoral vein two minutes later. Heart stopped by freezing one minute after radioactive erythrocytes injected. Endocardial surface exposed to x-ray film for several days. It can be seen that on the endocardial surface of the left ventricle there is a definite diminution in the amount of blood in the ischemic area, which is circled in white, as compared with the nonischemic portion of the same ventricle. In the right ventricle, there is no diminution in the amount of the blood in the ischemic area. It should be noted that radioactive erythrocytes are found in all parts of the ischemic portion. The surface outline of the right ventricle supplied by the anterior descending artery is narrower than indicated here.[13]

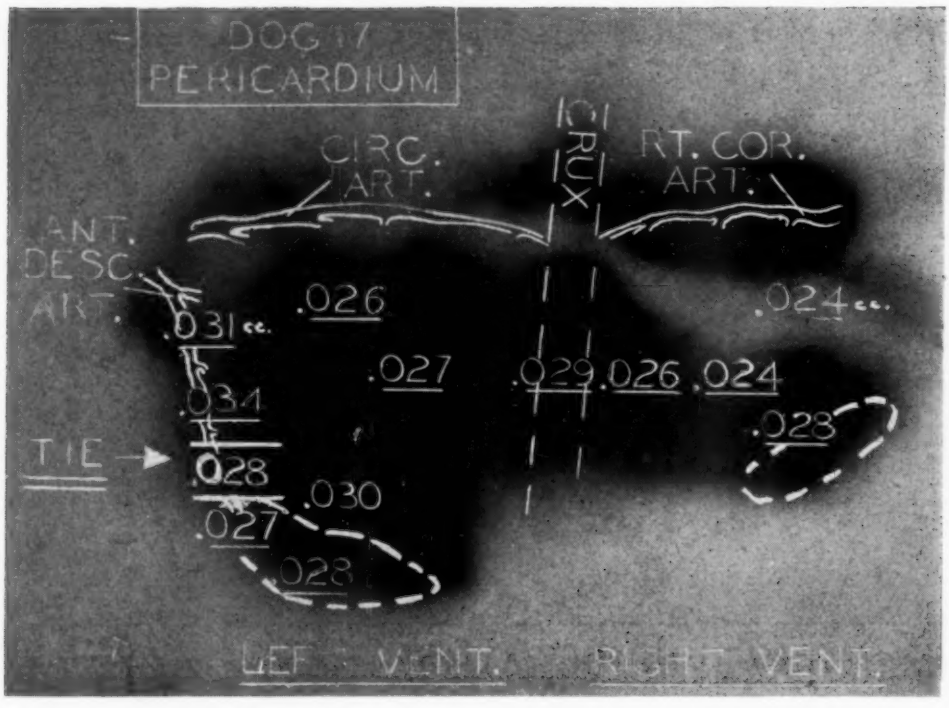


Fig. 8.—Radioautograph, pericardial surface, dog heart. Anterior descending branch of left coronary artery ligated near apex. Radioactive erythrocytes injected into femoral vein thirty minutes later. Heart stopped by freezing thirty-six seconds after injection of radioactive erythrocytes. Pericardial surface exposed to x-ray film for several days. On the pericardial surface of both the left and right ventricles it can be seen that the quantity of circulating blood is the same in the ischemic area distal to the tie as in the surrounding normal myocardium.

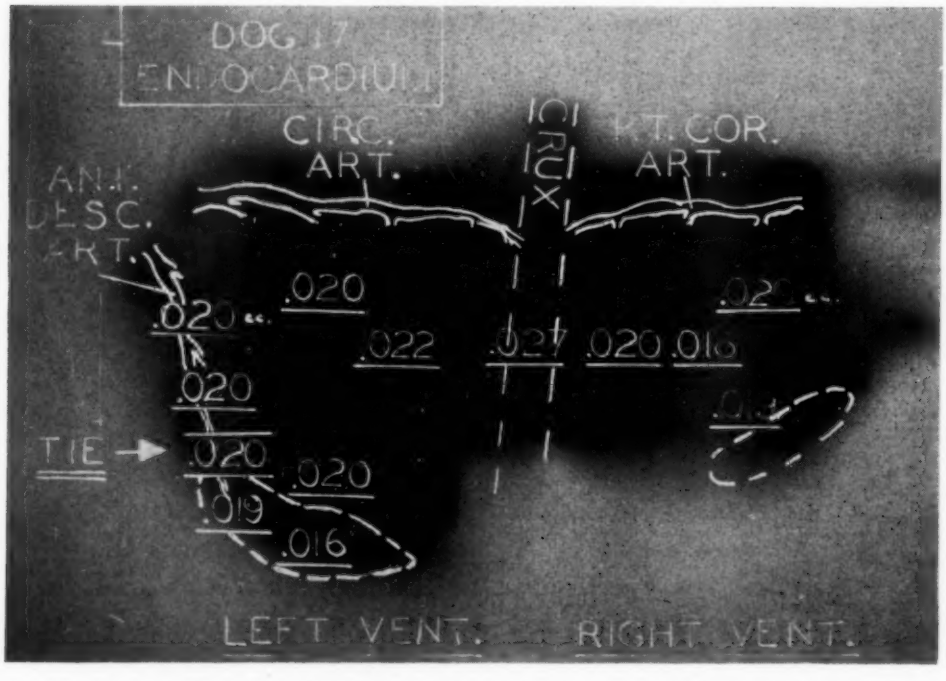


Fig. 9.—Radioautograph, endocardial surface, dog heart. Same dog heart as shown in Fig. 8. Endocarcial surface exposed to x-ray film for same length of time. It can be seen that, except for a small area of myocardium at the apex of the left ventricle, there was no diminution in the amount of blood on the endocarcial surface of the ischemic portion in the left ventricle when only a small segment of artery was occluded as in this animal.

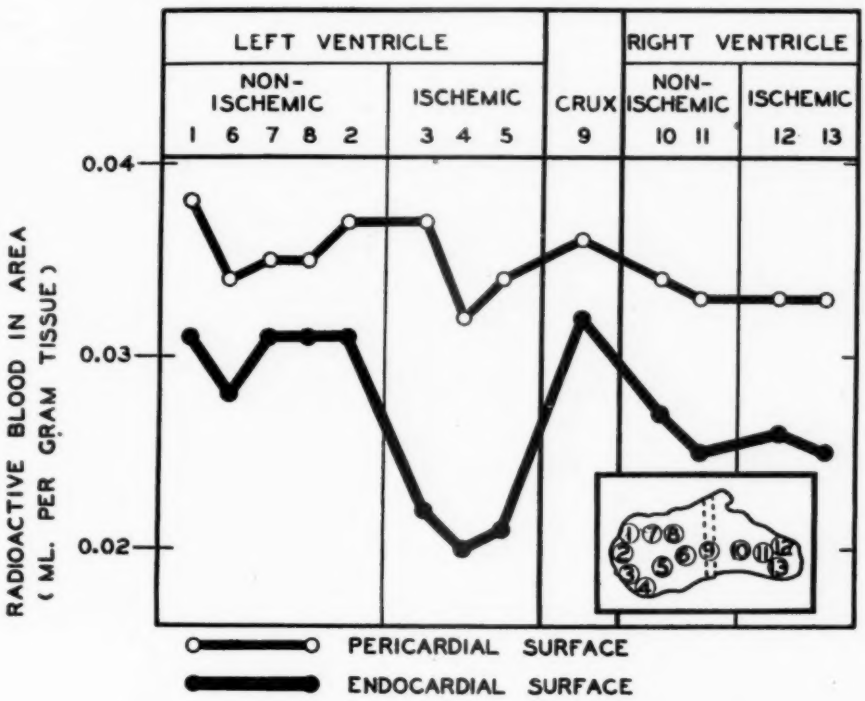


Fig. 10.—A graph summarizing the findings of the distribution and concentration of radioactive erythrocytes in the ischemic and nonischemic portions of the ventricular myocardium in the hearts of fourteen dogs with ligation of the left anterior descending artery. The average values for the amount of blood in the ischemic and nonischemic portions of the right and left ventricles are plotted in graph form. The location of the numbers which represent portions of myocardium measured is shown in the inserted diagram of the opened laid-out heart. The site of ligation of the left anterior descending artery is in or close to Area 2. It can be seen that there is no significant difference in the volume of blood found in the ischemic and nonischemic portions of the pericardial surface of the left ventricular myocardium. On the endocardial surface of the left ventricular myocardium, however, there is a significant reduction in the amount of collateral blood found in the ischemic portion as compared to the amounts of blood in the nonischemic portions of the same ventricle; this is statistically significant. There is no significant difference in the amount of blood in the ischemic and nonischemic portions of the right ventricular myocardium on either the pericardial or endocardial surface.

Evidence for the Active Circulation of Blood Through Collateral Vessels in the Ischemic Portion of Myocardium.—So far, our experiments had shown that collateral blood vessels supply blood to all portions of the ischemic myocardium, after ligation of the anterior descending artery. In spite of this, there was the possibility that this accessory blood failed to circulate actively, and was merely trapped in this region. If the collateral blood were stagnant it would serve no useful function in the nourishment of the ischemic muscle. It must be pointed out here that the radioactive red cell technique employed in these experiments for studying collateral circulation is not a measure of the rate of blood flow through a part, but rather a measure of the volume of blood contained in a particular portion of myocardium at the time of the determination, that is, at the moment when the heart is stopped by freezing. In order to find out whether the collateral

TABLE I. SUMMARY OF DATA OBTAINED BY GEIGER COUNTS OF INTRAVENOUSLY INJECTED RADIOACTIVE ERYTHROCYTES IN ARBITRARILY CHOSEN REGIONS OF THE HEARTS OF FOURTEEN DOGS AFTER I OF THE ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY

DOG NO.	TIME OF INJECTION AFTER ARTERIAL LIGATION (MINUTES)	TIME FROM INJECTION TO HEART FREEZE (SECONDS)	RADIOACTIVE BLOOD (ML. PER GRAM TISSUE)																							
			PERICARDIAL SURFACE													ENDOCARDIAL SURFACE										
			LEFT VENTRICLE									RIGHT VENTRICLE				LEFT VENTRICLE									RIGHT VI	
			NORMAL AREA				TIE	ISCHEMIC AREA			CRUX	NORMAL AREA		ISCHEMIC AREA		NORMAL AREA				TIE	ISCHEMIC AREA			CRUX	NORMAL AREA	
			1	6	7	8	2	3	4	5	9	10	11	12	13	1	6	7	8	2	3	4	5	9	10	11
4	7	300	0.016	0.016	0.012		0.016	0.017	0.016	0.016	0.011	0.012	0.012	0.010	0.015	0.014	0.015	0.018		0.012	0.009	0.010	0.011	0.015	0.026	0.014
6	3	150	0.030	0.028	0.033		0.029	0.020	0.022	0.022	0.038	0.024	0.026	0.030	0.030	0.023	0.020	0.024		0.026	0.016	0.017	0.015	0.024	0.028	0.020
7	2.5	120	0.075	0.074	0.105		0.073	0.079	0.074	0.058	0.121	0.117	0.099	0.100	0.122	0.092	0.067	0.101		0.093	0.039	0.053	0.041	0.105	0.067	0.069
8	2	60	0.029	0.030	0.025	0.028	0.034	0.035	0.027	0.043	0.022	0.022	0.014	0.017	0.013	0.018	0.022	0.015	0.021	0.027	0.025	0.018	0.030	0.023	0.014	0.015
9	1.5	35	0.047	0.036	0.038	0.040	0.037	0.041	0.042	0.034	0.033	0.043	0.045	0.045	0.027	0.050	0.037	0.042	0.045	0.038	0.030	0.028	0.025	1.045	0.050	0.044
10	2	25	0.024	0.022	0.023	0.026	0.023	0.030	0.022	0.026	0.021	0.019	0.019	0.017	0.016	0.016	0.019	0.025	0.023	0.019	0.018	0.018	0.018	0.021	0.022	0.016
11	2	65	0.027	0.039	0.024	0.038	0.027	0.023	0.019	0.025	0.039	0.035	0.026	0.022	0.019	0.039	0.038	0.042	0.036	0.033	0.022	0.019	0.029	0.026	0.020	0.029
12	2	55	0.038	0.035	0.025	0.022	0.036	0.030	0.037	0.035	0.032	0.030	0.031	0.026	0.035	0.026	0.027	0.024	0.027	0.021	0.020	0.012	0.023	0.023	0.019	0.017
13	2	40	0.104	0.062	0.074	0.113	0.065	0.072	0.068	0.082	0.062	0.053	0.062	0.081	0.067	0.047	0.032	0.035	0.052	0.050	0.033	0.037	0.025	0.037	0.036	0.038
14	2	60	0.015		0.014	0.016	0.020	0.019	0.017	0.020	0.017	0.019	0.021	0.021	0.021	0.012		0.012	0.014	0.014	0.007	0.007	0.005	0.011	0.014	0.014
15	7	71	0.050		0.051	0.043	0.068	0.046	0.034	0.043	0.041	0.043	0.045	0.039	0.034	0.043		0.035	0.042	0.046	0.041	0.024	0.034	1.039	0.031	0.031
17	30	36	0.033	0.027	0.026		0.028	0.027	0.028	0.030	0.029	0.026	0.024	0.024	0.028	0.020	0.022	0.020		0.020	0.019	0.016	0.020	0.027	0.020	0.018
19	30	27	0.020	0.016	0.013	0.020	0.017	0.017	0.017	0.017	0.012	0.014	0.012	0.014	0.016	0.014	0.018	0.017		0.016	0.012	0.011	0.013	0.015	0.014	0.012
21	5	600	0.029	0.024	0.024		0.038	0.028	0.025	0.024	0.025	0.020	0.021	0.021	0.023	0.020	0.019	0.019		0.023	0.016	0.016	0.016	0.022	0.016	0.017
		AVERAGE	0.038	0.034	0.035	0.035	0.037	0.037	0.032	0.034	0.036	0.034	0.033	0.033	0.033	0.031	0.028	0.031	0.031	0.031	0.022	0.020	0.021	0.032	0.027	0.025

In the pericardial portion of the left ventricle, comparison of the nonischemic regions 1, 6, and 7 with the ischemic regions 3, 4, and 5, as illustrated in Fig. 10, gave a P value g 0.6. Therefore, the volume of radioactive blood in the ischemic region of the pericardial portion of the left ventricle is statistically equal to that in the nonischemic region. In the portion of the left ventricle, comparison of the corresponding nonischemic and ischemic regions gave a P value less than 0.05. Hence, there is a significant reduction in the radioa volume of the endocardial regions of the left ventricle. The radioactive blood volume of the nonischemic and ischemic regions for both the pericardial and endocardial portions of th tricle was statistically equal (the P value in both cases was greater than 0.9).

blood actively circulated through the ischemic portions of myocardium the following experiments were performed.

Demonstration of Continuous Arterial Inflow Into Ischemic Region: If the collateral blood supplying the ischemic portion of myocardium were not actively circulating through this region, it would tend to stagnate in this region. If this were true, then radioactive erythrocytes, injected thirty minutes after coronary ligation, would either not appear or would be found in smaller amounts in this portion than with injection of the erythrocytes one and one-half minutes after ligation, because less or none could enter. On the other hand, if it could be shown that radioactive erythrocytes injected intravenously at intervals up to thirty minutes after ligation of the coronary artery were present in the area of ischemic myocardium in approximately the same quantities as at one and one-half minutes after the ligation of the artery, then it could be concluded that blood continues to supply the ischemic myocardium via anastomotic channels for a period of at least thirty minutes after acute coronary closure. That the latter is true is shown by the data in Fig. 11. The calculated ratio of volume of blood found in the ischemic

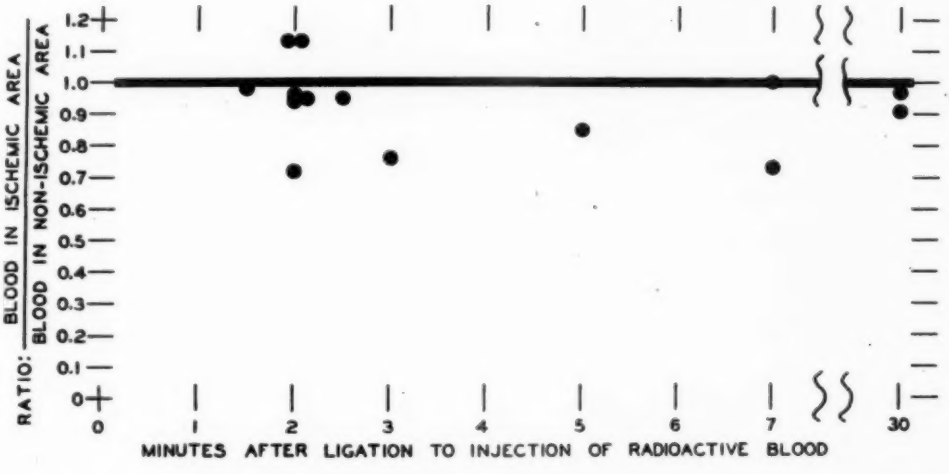


Fig. 11.—Graph showing that blood continues to enter the ischemic portion of myocardium via collateral channels up to thirty minutes after coronary ligation, the arbitrary time limit established for the experiment. The volume of blood per unit of tissue on the pericardial surface of the ischemic and nonischemic left ventricular myocardial portions was determined, and the ratio of the blood in the ischemic portion to the blood in the nonischemic portion was calculated. If the same amount of blood is found in the ischemic and nonischemic portions, the ratio would be 1.0. If, at thirty minutes, the ratio is less than at one minute, then it could be concluded that less blood gets into the ischemic portion at thirty minutes. However, the ratio at thirty minutes was the same as at one minute, showing that at thirty minutes, blood still entered the ischemic portion.

and nonischemic portions of the left ventricular myocardium are tabulated with respect to the elapsed time between ligation of the coronary artery and the intravenous administration of the labelled erythrocytes. The relative quantities of radioactive erythrocytes found in the ischemic myocardium were just as great at thirty minutes as at one and one-half minutes after ligation of the coronary

artery. This shows that blood derived from anastomotic vessels continues to enter the center as well as the periphery of the portions of ischemic heart muscle distal to the ligated artery for a period up to thirty minutes after experimental acute coronary occlusion in the dog.

Demonstration of Continuous Venous Outflow From Ischemic Region: In view of the fact that collateral blood continues to flow into the potentially infarcted portion of myocardium for a period of at least thirty minutes, it is logical to assume that it must also flow out. If it is assumed that the collateral blood entered this region and did not flow out, or if the outflow were slower than the inflow, then the longer the radioactive erythrocytes are allowed to circulate following their intravenous injection, the greater the quantity of radioactive erythrocytes that should be found in the ischemic myocardium. Thus, greater quantities of radioactive erythrocytes should be found in the ischemic portion of myocardium when the heart is stopped ten minutes after the injection of the labelled cells than when it is stopped twenty-five seconds after the injection. On the other hand, if the outflow of collateral blood from the ischemic portion kept pace with the inflow, there should be no accumulation of radioactive cells in this region with the passage of time following the injection of the labelled cells, and the quantities of radioactive erythrocytes found in this region should be no greater ten minutes after the injection of these cells into the systemic circulation than at twenty-five seconds.

In order to show that collateral blood entering the ischemic myocardium does not pool there but actively circulates, the data in this experiment were tabulated with respect to the time interval between injection of the labelled

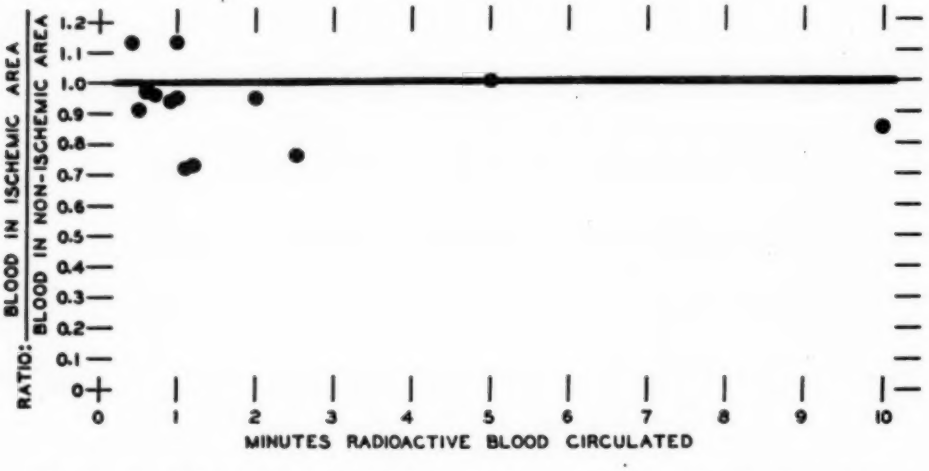


Fig. 12.—Graph showing that blood actively circulates through the ischemic area and does not stagnate there. Arranging the data in terms of the time between the injection of the radioactive erythrocytes and the time of stopping the heart, the ratio of the volume of blood in the ischemic and nonischemic portions on the pericardial surface of the left ventricular myocardium was determined, as in Fig. 11. If collateral blood did not actively circulate through the ischemic portion, but stagnated there, the ratio would be greater when the radioactive erythrocytes were allowed to circulate for ten minutes than if allowed to circulate for one-half minute. That blood was actively circulating through the ischemic area was shown by the fact that the same ratio was found at ten minutes as at one-half minute.

erythrocytes and freezing of the heart (Fig. 12). This time varied from twenty-five seconds to ten minutes. If the quantities of radioactive erythrocytes found in the ischemic myocardium were no greater ten minutes after their injection than at twenty-five seconds, then it can be concluded that blood entering the ischemic myocardium does not stagnate there but flows out. Examination of the data showed that this was true since the calculated ratio of volume of blood in the ischemic portion was no greater after radioactive erythrocytes had circulated for ten minutes than after circulating for twenty-five seconds.

In view of this observation that blood leaves the ischemic region through accessory venous channels when the artery is occluded, it is obvious that retrograde flow studies do not measure the entire collateral circulation and that the values obtained from such studies are not a true indication of blood supply to the ischemic region.[14]

These observations show that the collateral circulation to the myocardium of the dog which has been rendered ischemic by ligation of the anterior descending artery supplies all parts of the ischemic region. Furthermore, this collateral supply of blood circulates actively throughout the ischemic region.

PART III. TYPE OF COLLATERAL CIRCULATION FOLLOWING CORONARY OCCLUSION IN DOGS

In Parts I and II it was shown that after acute coronary occlusion in man and experimental acute occlusion of the anterior descending branch of the left coronary artery in dogs, there is a continuous actively circulating collateral blood flow in the portion rendered ischemic by occlusion of its major artery. These experiments, however, did not demonstrate the source of the collateral blood. There are three possible sources: (1) Extrapericardial or pericardial anastomotic vessels, (2) the Thebesian-luminal group of vessels, and (3) anastomotic channels from the other coronary arteries. In these animal experiments, the pericardium was opened and reflected, and there is no reason to assume that pericardial anastomoses played any part in the blood supply to the ischemic region.

To determine which of the remaining two possible sources is responsible for the collateral circulation of the heart following acute coronary occlusion in the living animal, fluorescein was injected into the femoral vein of dogs, and high-speed color cinematographic studies were made of the heart. Under special lighting, the fluorescein imparts a greenish-yellow color to the normally reddish-brown myocardium. By observing the manner in which the fluorescence appeared and spread over the ventricular myocardium, the hemodynamics of the collateral circulation immediately following acute coronary occlusion in the dog could be visually demonstrated. Early studies of the heart by means of cinematography were made by Takeuchi[15] and Strughold;[16] more recent studies were made by Landis and associates,[17] Burchell and Visscher,[18] and Gray.[19] High-speed color photography provides much information impossible to obtain by direct observation, because the heart is greatly magnified when the films are projected, slow motion provides increased detail, the entire process, as well as a

single heart beat, can be repeatedly studied, and specified effects can be obtained with special lighting or film sensitive to a selected color.

Details of Method.—Dogs were anesthetized with sodium pentobarbital administered intravenously. The heart was exposed as described in Part II. High-speed motion pictures of the heart were made at 48 to 64 frames per second on Kodachrome film, using a specially built 16 mm. camera with a rack-over device which permitted precise alignment to allow sharp focus when the camera was approximately three feet distant from the heart. The field was photographed under incandescent light and, when necessary, special light filters were added to transmit a wave length under which fluorescein was visible.[20]

In each experiment the heart was photographed before, during, and after ligation of the anterior descending branch of the left coronary artery, and during injection into the femoral vein of 10 ml. of a 5 per cent solution of the sodium salt of fluorescein. Forty-five seconds to one minute after the fluorescein injection, contractions of the heart were stopped with the freezing mixture described in Part II.

The films were carefully and repeatedly studied by projection with great magnification at one-fifth the speed of the original heart rate.

Results.—

Spread of Fluorescence in Normal Hearts: Following intravenous injection of fluorescein, the yellow-green fluorescence appeared in the major coronary arteries in five to seven seconds, and then spread very rapidly over the adjacent myocardium. Maximal filling occurred within ten to sixteen seconds.

Spread of Fluorescein in the Ischemic Area: In hearts with the anterior descending branch of the left coronary artery ligated, the first thing noted following the intravenous administration of fluorescein was that the circumflex branch of the left coronary artery, the anterior marginal artery, and the anterior descending branch of the left coronary artery up to the point of the ligature became bright yellow in color. Beyond the ligature the anterior descending branch retained its normal color; that is, it did not fill with the yellow fluorescent blood. The yellow fluorescence then rapidly spread over the surface of the myocardium adjacent to the fluorescent nonligated vessels and appeared to surround the reddish-brown surface area of the ischemic myocardium. By concentric filling, the ischemic surface area became as intensely yellow as the rest of the heart in fifteen to thirty seconds (Fig. 13).

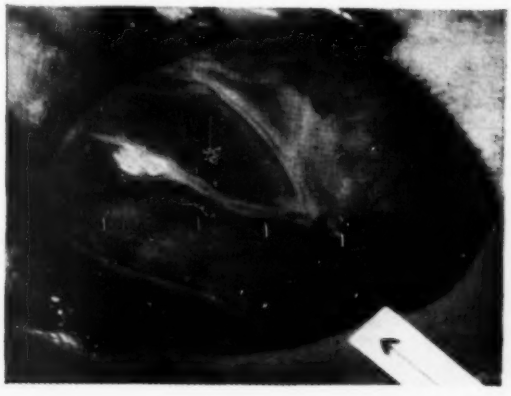
On section of the ischemic left ventricular myocardium, it was observed that the yellow fluorescence was intense on the subpericardial portion of the cut surface, which appeared bright yellow-green. The subendocardial portion, however, retained a reddish hue and appeared less intensely fluorescent, indicating incomplete filling of this portion of the myocardium with the fluorescent blood (Fig. 14).

The portion of the right ventricle adjacent to the anterior interventricular sulcus and to the right of the ligated anterior descending artery immediately became fluorescent upon the first sweep of the dye over the surface of the heart.

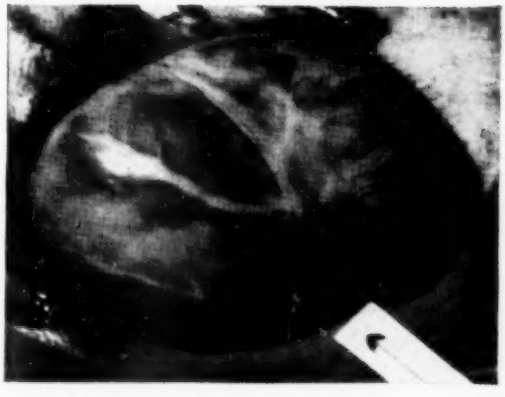
Fig. 13.—Dog heart with anterior descending branch of left coronary artery ligated. Arrow denotes ligature about artery. Individual frames from motion pictures of heart at time of injection and at subsequent intervals show concentric type of filling of ischemic region via interarterial anastomoses. Ischemic region completely filled in sixteen seconds. The ischemic portion of the right ventricle became fluorescent as rapidly as the nonischemic portion of the right ventricle.

A, Time of intravenous injection of fluorescein.
B, Six seconds after fluorescein injection.
C, Nine seconds after fluorescein injection. Note beginning concentric filling about ischemic region.
D, Eleven seconds after fluorescein injection. Ischemic region partially filled.
E, Thirteen seconds after fluorescein injection. Filling almost complete.
F, Sixteen seconds after fluorescein injection. Filling complete.

A



B



C

D

E

F

The spread of the fluorescein to the right ventricle was so rapid that it was impossible to tell the manner in which the fluorescein arrived in the ischemic portion of the right ventricle. That this portion of the right ventricle, which derives its blood supply from the ligated artery and is supposedly ischemic, filled as rapidly as the nonischemic myocardium and much more rapidly than the ischemic left ventricle is consistent with the findings in the previous experiment. It was shown that this ischemic portion of the right ventricle contained on both its perciardial and endocardial sides collateral blood equal in amount to the blood in nonischemic portions of the right ventricle.

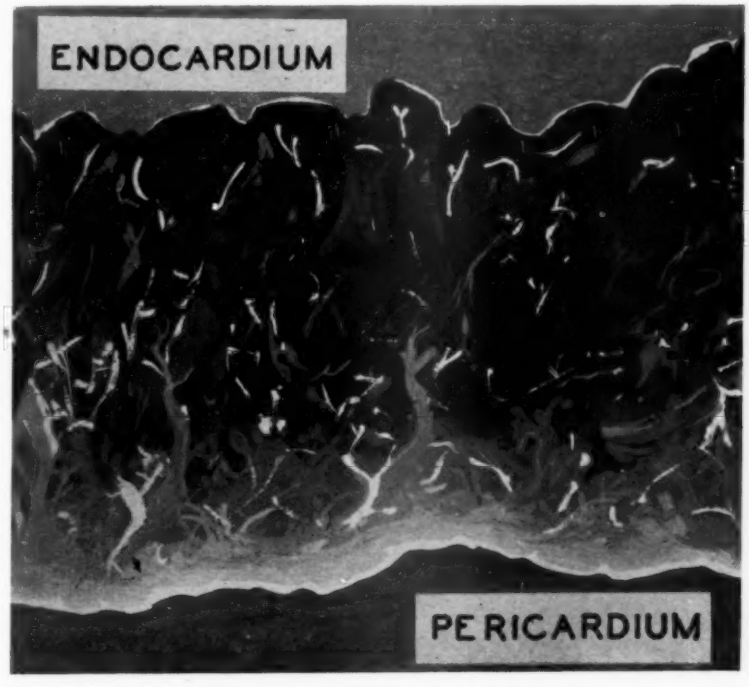


Fig. 14.—Drawing of cut section of ischemic region of left ventricle. Fluorescein was injected intravenously after ligation of the anterior descending artery near its origin. Note that pericardial portion of myocardium is light, denoting good filling with fluorescein (via interarterial anastomoses). The lightness due to the fluorescein becomes less and less intense as the endocardial portion is reached, indicating little filling with fluorescein.

It is concluded, first, that collateral blood entering the ischemic myocardium of the left ventricle is largely, if not entirely, supplied by interarterial anastomoses between the adjacent coronary arteries and the terminal branches of the ligated artery. The pericardial anastomoses have been dismissed as a source of blood for the ischemic myocardium in this experiment because the pericardium was opened and reflected to expose the heart. If the Thebesian-luminal group of vessels supplied the major part of the collateral blood to the ischemic myocardium, the yellow color should have appeared in all parts of the ischemic portion simultaneously after the spread of the color over the rest of the myocardial

surface, and the yellow fluorescence should have been more intense on the endocardial aspect of the cut surface of the ischemic left ventricular myocardium than on its pericardial aspect. This is in contrast to the actual observations of concentric encroachment on the red ischemic myocardium by the surrounding yellow color and the more intensely yellow fluorescence on the subpericardial aspect of the cut surface.

Second, when the anterior descending branch of the left coronary artery is suddenly occluded, the portion of the right ventricular myocardium supplied by the occluded artery has a much better collateral blood supply than the ischemic region of the left ventricle. This was shown by the rapid filling of the ischemic right ventricular myocardium with the fluorescent blood and by the large quantities of radioactive erythrocytes entering this part of the heart demonstrated in Part II. These findings are consistent with the common observation by pathologists that the occurrence of an infarct in the right ventricle is rare. This will be discussed more fully later.

These observations prove that the collateral circulation to the ischemic region of the dog heart with a ligated coronary artery is through interarterial anastomoses.

Effect of Site of Tie.—The degree of filling of the ischemic myocardium by the fluorescent dye is influenced by two major factors: (1) the site at which the anterior descending artery is ligated with respect to the distance from its point of origin, and (2) the mean arterial blood pressure at the time of the arterial occlusion. The effect of low blood pressure, as in shock, on the degree of collateral circulation to the ischemic myocardium will be the subject of another paper. In the experiments reported in this communication, an effort was made to maintain the blood pressure within normal limits and the major factor influencing the extent of filling of the ischemic myocardium by collateral blood was the point at which the artery was ligated.

If the artery was tied close to its point of origin, filling of the ischemic surface area with the yellow fluorescence was incomplete and often the center of the ischemic area appeared to have little fluorescence compared with the rest of the ischemic area. The area of partial filling was located near the apex on the anterior wall of the left ventricle and was about 1.75 cm. in diameter.

If the artery was tied further from its origin, more than one-half the distance between its origin and termination at the apex, the ischemic surface area of myocardium was always completely and rapidly filled with the dye; and the intensity of the yellow fluorescence was just as great as that of the surrounding nonischemic regions (Fig. 13, *F*).

It may be concluded that the more distal the occlusion, the better is the relative filling of the ischemic myocardium. But even with ties close to the point of origin of the vessel, there is an effective collateral circulation because the fluorescent blood enters the ischemic area especially at its periphery. The clinical significance of this observation will be discussed later.

Cyanosis of Ischemic Myocardium.—With the use of motion picture film sensitive to blue color, cyanosis of the ischemic myocardium was easily detected.

In some hearts, cyanosis did not seem to appear at all; in other hearts, it appeared almost immediately after ligation.

Usually the surface area of the portion of right ventricle normally supplied by the anterior descending branch was not cyanotic and retained its bright red color. Occasionally 1 or 2 mm. of this area, and rarely a more extensive area, appeared cyanotic.

The area of cyanosis on the left ventricle was variable. In most instances the area of cyanosis was less than the area supplied by the anterior descending branch of the left coronary artery (Fig. 15). In a few instances the cyanosis involved approximately the entire area normally supplied by the occluded artery. Possibly, in these experiments with less extensive cyanosis, the blood pressure and general condition of the animal remained better than in those with a larger area of cyanosis. The reasons for this will be presented in another paper.

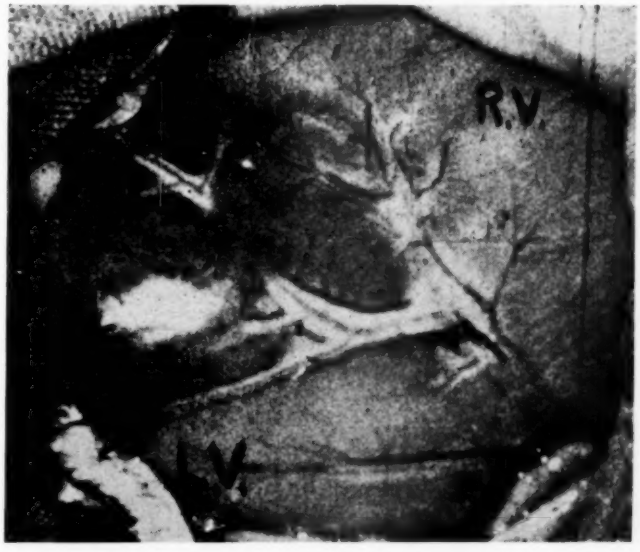


Fig. 15.—Dog heart after ligation of anterior descending branch of left coronary artery. The area of cyanosis on both the right and left ventricles, the darker zone, is smaller than the area supplied by the occluded artery.

L.V. = Left ventricle
R.V. = Right ventricle

The fact that the area of cyanosis following occlusion of the anterior descending branch of the left coronary artery was smaller than the area supplied by this artery demonstrates that oxygenated arterial blood entered the area through collateral vessels. Furthermore, the source of this blood must be the adjacent coronary arteries, through intercoronary anastomotic channels, because of the absence of cyanosis at the periphery of the area supplied by the ligated artery. This reasoning is the same as that applied to the manner in which fluorescein entered the ischemic area. The usual presence of cyanosis, in spite

of the fact that blood enters and leaves the ischemic area, indicates that the total circulation and the rate of flow are less than in other portions of the myocardium. The occurrence of cyanosis, however, is not incompatible with an active arterial circulation in the ischemic area, as demonstrated in Part II.

DISCUSSION

Function of the Collateral Circulation.—It has been demonstrated in several ways in the present study that actively circulating collateral blood supplies the ischemic myocardium *immediately* following acute coronary occlusion. Since myocardial infarction is a common sequela of coronary occlusion, does the anastomotic circulation, as it exists, serve any useful function in this situation?

It is the belief of the authors that this collateral circulation performs the following functions: (1) It nourishes the entire ischemic portion of myocardium, including the center, with the result that this portion is strengthened, and occurrence of cardiac rupture and aneurysmal dilatation after myocardial infarction are less frequent than expected; (2) as a corollary of the preceding function, it allows healing to take place in the portion of ischemic and necrotic myocardium, with the subsequent development of a firm scar; (3) it is important in determining the location of the infarct which develops after acute coronary occlusion; (4) it plays a part in determining the shape and configuration of the resultant infarct; (5) it limits the size of the resultant infarct; and (6) the available anastomotic channels enlarge in the course of time because of the favorable pressure gradient established following coronary closure. Each of these functions will be discussed more fully. The enlargement of the anastomotic circulation subsequent to long-standing complete coronary occlusion or to gradual narrowing of the coronary arteries has been well established in studies by other investigators,[21,22] and requires no further comment here.

Role of the Collateral Circulation in the Prevention of Cardiac Rupture: If there were no collateral circulation supplying the ischemic portion of myocardium after acute coronary occlusion, cardiac rupture should occur in every case in which a sizable myocardial infarct develops. Actually, rupture of the heart is a relatively uncommon event, with an incidence varying from 5 to 10 per cent.[23] It is believed, then, that the collateral circulation available after acute coronary occlusion is largely responsible for preventing cardiac rupture in most cases of myocardial infarction. It was shown in this study that collateral blood supplied all parts, including the center, of the potentially infarcted myocardium. However, the rate of blood flow and total volume of blood through the ischemic myocardium must be diminished and the collateral circulation insufficient, because death of muscle occurs. Evidence for this includes (1) the cyanosis of the ischemic myocardium (Part III), (2) the incomplete filling of the ischemic myocardium with fluorescein when the anterior descending artery was tied close to its origin (Part III), (3) the delayed but complete filling of the ischemic myocardium with fluorescein when the anterior descending artery was tied more distally (Part III), and (4) the diminished amount of radioactive red cells in the endocardial portion of the left ventricle (Part II).

On histologic examination, the pathologic changes which appear in a myocardial infarct include an intense invasion of the region of the necrotic myocardium by leucocytes, and the appearance of fibrin and edema. Such manifestations require the presence of a blood supply in this region, and may help to explain why healing rather than rupture of a myocardial infarct usually occurs. Furthermore, an afferent circulation to the region of the infarct must be present to supply the vehicle by which dead muscle tissue in various stages of disintegration is removed. Thus, although the collateral blood supply is insufficient to prevent muscle death in an actively working organ, yet this blood supply strengthens the portion of ischemic myocardium by limiting the size of the infarct, preventing necrosis of all of the muscle fibers in the part involved, and promoting healing processes. Moreover, it should be emphasized that an immediately functioning anastomotic circulation is necessary for this purpose, because cardiac rupture usually occurs within the first two weeks after onset of the clinical symptoms of acute coronary occlusion.

Correlation of Known Pathologic Observations With the Experimental Findings: The findings in the present investigation can be correlated with, and may serve to explain, many of the well-known observations concerning the location, shape, and size of myocardial infarcts occurring as a consequence of acute coronary occlusion. A study of the collateral circulation immediately following acute obstruction of a major coronary artery is pertinent because infarction occurs within a few hours after the onset of prolonged ischemia, long before the development of the extensive functioning collateral circulation which has been demonstrated in hearts with long standing coronary occlusion or gradual narrowing of one or more major coronary arteries.[21,22]

It should be pointed out, however, that the extent of the collateral circulation found in the dog's heart following acute coronary occlusion is not entirely comparable to that occurring in human hearts following acute coronary occlusion. In the dog, the coronary arteries are normal, while in man, coronary arteriosclerosis of most or all of the major coronary arteries almost always precedes acute coronary occlusion for a relatively long period of time. It is well known that there is an intense vascular congestion in the ischemic myocardium of arteriosclerotic human hearts (Fig. 3). It is often stated that vessels in this region represent newly developed vascular channels, but it is our belief, in view of the abundant collateral circulation, that these "new" blood vessels are merely enlarged or enlarging pre-existent vessels. When one of the coronary arteries is gradually occluded, the arterial pressure distal to the stenosis or occlusion diminishes, and thus a pressure gradient is established which allows blood to flow from the opposite coronary artery through the existent anastomotic channels. In this way, a more efficient collateral circulation develops by the enlargement of pre-existent anastomotic channels. Thus, the collateral circulation to ischemic human heart muscle following complete occlusion of a coronary artery which has been narrowed for a long time should be greater than that found in the dog's heart.

However, if gradual occlusion or narrowing occurs simultaneously in both coronary arteries, there is presumably no pressure gradient and the function of the anastomotic channels between these arteries is, therefore, limited after occlusion of one of the coronary arteries. In this case, the functional capacity of the collateral circulation following occlusion of one of the coronary arteries is comparable to that in the dog's heart in which there is no pressure gradient previous to the coronary occlusion. The development of arteriosclerosis in the intercoronary anastomoses with resultant narrowing or occlusion of these channels, as suggested by Roberts,[24] could also limit their functional capacity. Thus, in the human heart, there may be factors which both aid and suppress the effective collateral circulation. Fortunately, in the human heart, the factors which aid the development of effective collateral circulation are generally more abundant than those which suppress it.

Location of Infarct: Despite the fact that occlusions are not significantly more numerous in the left than in the right coronary arteries,[27] myocardial infarcts are much more frequent in the left ventricle and septum than in the right ventricle.[23, 25-28]

In this connection, Whitten[29] found that the deep branches of the arteries of the left ventricle leave the main trunks at right angles and pass directly through the myocardium, whereas the arteries of the right ventricle spread out in practically the same plane as the larger artery from which they arise. He suggested that the far greater occurrence of infarction in the left ventricle may be related to the difference in the anatomic structure of the arteries in the muscle of the two ventricles. The very rare occurrence of infarction in the right ventricle is indeed striking. For example, the artery which was experimentally occluded in this study was the anterior descending branch of the left coronary artery which, in the dog, supplies the anterior aspect of the left ventricle, the interventricular septum, and a narrow band of myocardium on the anterior aspect of the right ventricle adjacent to the anterior longitudinal groove down to the apex.[13] Nevertheless, occlusion of this artery rarely results in an infarction in the right ventricular wall, but almost always the resultant infarct is found in the anterior wall of the left ventricle, near the apex. In man, these findings also hold true for the hearts in which the left coronary artery is predominant, a pattern which Schlesinger[30] has shown to be the usual one in the dog's heart.

Since, under these circumstances, myocardial infarction rarely occurs in the right ventricle, it must be concluded that the collateral circulation to the right ventricle is usually adequate to prevent the development of myocardial necrosis. Further evidence testifying to the good collateral blood supply of the right ventricle may be obtained from some of the results of the experiments described in this paper. After acute experimental occlusion of the anterior descending branch of the left coronary artery, it was found that: (1) In the colored motion pictures cyanosis was usually absent or minimum in amount on the anterior surface of the right ventricle as compared with the usually extensive area of cyanosis on the anterior aspect of the left ventricle (Part III); (2) the entire

right ventricular myocardium was rapidly and completely filled with the yellow fluorescent blood as compared with the frequently incomplete staining of the anterior surface of the left ventricular wall (Part III); and, finally, (3) there were equal volumes of radioactive erythrocytes on both the pericardial and endocardial sides of the "ischemic" portions of right ventricular wall as compared with the respective surfaces of the nonischemic portions of the right ventricle; in the left ventricle, however, the endocardial side of the ischemic portions always contained significantly smaller quantities of radioactive erythrocytes than the same side of the nonischemic portion (Part II).

The interarterial anastomoses were shown to be the source of the collateral blood supply to the ischemic region of the left ventricle following occlusion of the anterior descending coronary artery. However, the findings in these experiments did not reveal the source of the abundant collateral supply to the portion of the right ventricle normally supplied by the occluded artery, since the fluorescein entered the right ventricle too rapidly to reveal its source. Roberts and Loube[31] reported a case of a single congenital right coronary artery in which infarction of the right ventricle followed thrombosis of the arterial branch supplying the right ventricle. Necropsy in this case revealed that the branches of the single coronary artery supplying the left ventricle were markedly stenotic, so as to limit the adequacy of the interarterial anastomoses between the artery to the left ventricle and the thrombosed artery to the right ventricle. If the collateral blood supply to the right ventricle were from a source other than the interarterial anastomoses, then, in this case, the right ventricle should not have become infarcted. Thus, the source of collateral blood to ischemic myocardium of the right ventricle would appear to be the same as that to ischemic myocardium of the left ventricle, that is, interarterial anastomoses.

Shape of the Infarct: It has been commonly observed[25,27,32] that the apex of a myocardial infarct is directed toward the epicardial surface and the base toward the endocardial surface of the ventricular wall. The finding that there is a greater involvement of the ventricular wall on its subendocardial than upon its subepicardial surface has been confirmed by recent studies[33,34] on the correlation of electrocardiographic and pathologic findings in myocardial infarction of the left ventricle. Furthermore, Master and associates[35] have shown that the pathologic picture of acute coronary insufficiency without acute coronary occlusion is one of subendocardial focal necrosis involving primarily the posterior wall, septum, and papillary muscles of the left ventricle; this may vary from microscopic lesions to a more extensive predominantly subendocardial infarction. The data obtained in the present studies offer an adequate explanation for these well-known pathologic observations. It was shown that the pericardial side of the potentially infarcted portion of left ventricular myocardium had a better collateral blood supply than the endocardial side. It can be seen that the effectiveness of the collateral circulation at these sites, as was demonstrated in this study, is an important factor in determining the configuration of the infarction that subsequently develops. It is suggested that the reasons for the unequal nourishment of the pericardial and subendocardial portions of the left ventricular

myocardium by collateral blood are probably (1) the fact that the coronary arteries and their major branches lie on the epicardial side, and then dip into the deeper portions of the myocardium where they arborize, and (2) the great thickness of the left ventricular wall. The observation[27] that there is usually a thin endocardial layer of preserved muscle tissue underlying the base of an infarct suggests that the intraventricular blood bathing the endocardial aspect of the ventricular wall nourishes this portion of the myocardium, possibly through the Thebesian vessels. However, the Thebesian vessels are certainly inadequate for the nourishment of the greater portion of the left ventricular myocardium immediately after acute coronary occlusion, as shown by findings in these studies and by the configuration of the resultant infarct.

The Size of the Infarct: It has long been known that a myocardial infarct is smaller than the muscle supplied by the obliterated vessel. This has been demonstrated in man[25,36,37] and in the dog.[38] Meneely and co-workers[39,40] established that increased capillary permeability to trypan blue occurred in ischemic myocardium, but found that the region showing evidence of increased capillary permeability was smaller than that region normally supplied by the occluded artery. Similar observations were made in the present study, in which it was shown that if acute coronary closure occurred at the distal portion of the artery, the collateral circulation was sufficient to supply adequately the ischemic myocardium, but if the proximal portion of the artery was acutely occluded, the collateral circulation was effective only to the extent of limiting the region of relative ischemia.

Because of the favorable pressure gradient which develops following acute coronary occlusion, the collateral circulation is able to nourish the ischemic portion, as has been already shown. Although the collateral circulation is sufficient to maintain the integrity and viability of heart muscle at the periphery of the ischemic portion, it is not sufficient to prevent myocardial necrosis in the center. This can be explained by the nature of the pressure gradient between the adjacent coronary arteries and the occluded artery. The pressure in the collateral vessels is highest at the periphery of the ischemic region and declines as the center of the ischemic part is approached. Therefore, if shock is not a complicating factor, a zone of viable muscle at the periphery of the ischemic portion is always found. Assuming no hemodynamic changes, the viable zone of tissue measured in depth from the periphery toward the center should remain the same whether a large or small arterial segment is occluded. Consequently, the mass of necrotic tissue which subsequently develops is not directly proportional to the total mass of myocardium supplied by the occluded artery. If a small arterial segment is occluded, there may be no necrosis, or, at most, a small amount of subendocardial necrosis. However, if a large portion of the artery is occluded, the necrotic mass is much larger, even though the zonal mass of viable tissue is proportionately the same. This is shown diagrammatically in Fig. 16. In this case, when a large part of an artery was occluded, 48 per cent of the total ischemic portion was necrotic, whereas when a smaller arterial segment was occluded, only 20 per cent of the total ischemic portion was necrotic. Thus,

when a greater portion of an artery is occluded, the resulting infarct is proportionately greater in size than when a small portion of an artery is occluded. Actually, in life, when a large portion of myocardium is rendered ischemic by coronary occlusion, shock often occurs with its attendant drop in blood pressure, and the pressure gradients necessary for collateral blood flow are correspondingly diminished. The possibility is now being investigated that a larger mass of necrotic tissue will result under these circumstances.

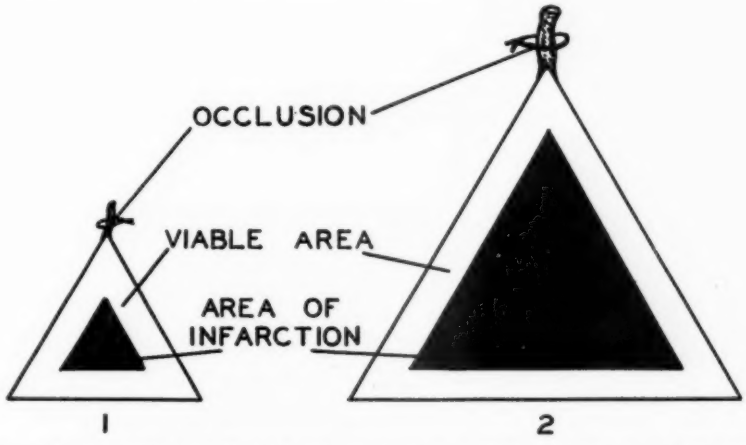


Fig. 16.—Diagrammatic, two-dimensional representation of the size of infarct following occlusion of (1) a small coronary artery, and (2) a large coronary artery. The viable area extends an equal distance from the periphery of the ischemic area to the area of infarction in both cases, however, the infarcted area in 2 is a much larger percentage of the total ischemic area than that in *1*. This can be exp'ained by the fact that collateral circulation to the area enters from interarterial anastomoses.

The Role of the Thebesian-Luminal Group of Vessels in the Collateral Circulation: There has been much speculation and uncertainty regarding the functional significance of the Thebesian and arterioluminal vessels in the circulation of the heart. This has been especially true with respect to their possible role as collateral channels permitting nourishment of the myocardium following the occurrence of coronary occlusion. It is conceivable that this group of vessels could serve as arterial channels from the left ventricular cavity to the ischemic myocardium after left coronary occlusion, especially since the pressure gradient would be favorable for the passage of intraventricular blood in this direction during systole. Several pieces of evidence suggest that this is possible. Pratt[41] found that it was possible to keep a mammalian heart beating by perfusing blood through the Thebesian vessels. When dye was injected into the right ventricle in brief experiments, it was found that extensive capillary injection of the myocardium occurred if the right ventricular pressure exceeded the left ventricular pressure.[42] Leary and Wearn[43] reported two cases which showed that complete occlusion of the ostia of both coronary arteries was compatible with an active life, and they suggested that the integrity of the heart muscle was maintained in these persons by an anastomotic circulation through the Thebesian vessels. On the other hand, Stella[44] and Gregg[45] were unable to demonstrate a blood flow

from the ventricles into the coronary arteries or superficial venous system after temporary functional separation of one or all coronary arteries from the aorta.

In the present experiments, it appeared that the collateral blood supplying the potentially infarcted portion of myocardium immediately after coronary artery ligation was derived from the adjacent coronary arteries through interarterial anastomoses, rather than from the ventricular cavity through the Thebesian-luminal group of vessels. The evidence for this view was based upon the following observations: (1) The concentric manner in which the fluorescein stained the ischemic myocardium; (2) the greater intensity of the yellow fluorescence on the subpericardial aspect of the cut surface of the ischemic myocardium than on the subendocardial aspect; (3) the incomplete filling with fluorescein of the central portion of the ischemic myocardium following ligation of the anterior descending artery near its origin; and (4) the significant diminution in the quantities of radioactive erythrocytes contained on the endocardial side of the ischemic portion of myocardium, a finding not obtained on the pericardial side of this region.

Although the present studies indicate that the Thebesian-luminal group of vessels is not responsible for the collateral blood supply of the ischemic myocardium immediately after occlusion of the anterior descending artery, yet they do not preclude the fact that these vessels may subsequently enlarge and function as sources of collateral blood supply to the infarcted myocardium, as suggested by Wiggers[3] and by the observations of Leary and Wearn.[43]

SUMMARY AND CONCLUSIONS

1. Studies on collateral circulation in living human and dog hearts with coronary occlusion are presented.

2. One method of study was based on the use of labelled erythrocytes as tracer constituents of circulating blood. Saline suspensions of erythrocytes labelled with radioactive phosphorus were injected intravenously into moribund patients shortly before death. After death, the hearts were removed, and the distribution of radioactive red cells was determined quantitatively in arbitrarily chosen portions of the hearts.

3. In normal human hearts, and in arteriosclerotic human hearts with myocardial infarction, the radioactive red cells were distributed evenly throughout the ventricular myocardium in the infarcted as well as in the uninvolved myocardium. These findings demonstrate the presence of a functioning collateral circulation to all parts of a myocardial infarction in the arteriosclerotic heart in living man.

4. Saline suspensions of erythrocytes labelled with radioactive phosphorus were injected intravenously into dogs at various periods after ligation of the anterior descending branch of the left coronary artery. At various intervals after the injections, the hearts were stopped suddenly by freezing. The distribution and concentration of radioactive red cells were quantitatively determined in arbitrarily chosen portions of the myocardium.

5. Radioactive erythrocytes were found in all parts of the hearts of both normal dogs and dogs with acute occlusion of the anterior descending artery, demonstrating that blood from collateral channels supplies the entire mass of ischemic myocardium distal to a ligated coronary artery.

6. In the left ventricle, the calculated volume of blood in the subepicardial portion of the ischemic myocardium was equal to that in the contiguous nonischemic subepicardial myocardium. In the subendocardial portion of the left ventricle the volume of blood in the ischemic myocardium was about two-thirds of the volume of blood in the nonischemic subendocardial myocardium. Thus, the subepicardial portion of the ischemic myocardium of the left ventricle is better nourished by collateral circulation than the subendocardial portion.

7. Both subepicardial and subendocardial portions of the ischemic region of the right ventricle normally supplied by the ligated anterior descending artery contained volumes of blood equal to those in nonischemic regions of the right ventricle, showing that the ischemic right ventricular myocardium normally supplied by the ligated anterior descending artery is better nourished by collateral blood than a similar portion of the left ventricle.

8. The ratio of blood found in the ischemic myocardium to that found in the nonischemic myocardium was just as great at thirty minutes as at one and one-half minutes after ligation of the anterior descending artery, showing that anastomotic blood continues to enter the ischemic myocardium for at least thirty minutes after experimental sudden coronary occlusion in the dog.

9. The ratio of blood in the ischemic region to blood in the nonischemic region was no greater after radioactive erythrocytes had circulated for ten minutes than for twenty-five seconds, showing that blood entering the ischemic region flows out. Thus, the collateral blood supply to ischemic myocardium is an actively circulating one, which supplies the entire ischemic region.

10. The second method of study was based on slow motion cinematography of the exposed beating dog's heart, under special lighting, which made fluorescein visible. Fluorescein was injected intravenously in normal dogs and in dogs with occlusion of the anterior descending artery.

11. In normal dog hearts, the yellow fluorescence appeared in the major coronary arteries in five to seven seconds and then spread rapidly over the adjacent myocardium with maximum filling at ten to sixteen seconds.

12. In dog hearts with the anterior descending artery ligated, the fluorescein appeared in the nonischemic left ventricular myocardium in a similar fashion to its appearance in the normal dog heart, and in fifteen to thirty seconds the ischemic left ventricular myocardium became as intensely yellow as the rest of the heart. The ischemic myocardium filled concentrically. The subendocardial portion of the ischemic left ventricular myocardium was less completely filled with fluorescein than the subepicardial portion. These findings show that the intercoronary anastomoses were the major source of collateral blood to the ischemic myocardium. The smaller the ischemic region, the better was the filling of the ischemic myocardium in the left ventricle.

13. The portion of the right ventricle normally supplied by the ligated artery filled with fluorescein as rapidly as the nonischemic myocardium and more rapidly than the ischemic myocardium of the left ventricle, confirming the fact that this portion of the right ventricular myocardium has a much better collateral blood supply than the ischemic portion of the left ventricle.

14. Cyanosis of the ischemic myocardium following ligation of the anterior descending artery was observed by means of motion pictures of the dog's heart with film sensitive to blue color.

15. The area of cyanosis on the left ventricle was usually less extensive than the surface area of the myocardium normally supplied by the ligated vessel. The absence of cyanosis at the periphery of the ischemic region indicated that the intercoronary anastomotic channels were the source of blood to the ischemic region. The ischemic portion of the right ventricle was not usually cyanotic, confirming the fact that the anastomotic blood supply to the ischemic portion of the right ventricle is better than that to the ischemic portion of the left ventricle. The presence of cyanosis in the ischemic myocardium, which was shown to have an actively circulating blood supply, shows that the rate of flow in this region was less than in normal myocardium.

16. Actively circulating blood from intercoronary anastomoses supplies the myocardium rendered ischemic by acute coronary occlusion. This blood supply prevents the more frequent occurrence of cardiac rupture and aneurysmal dilatation and promotes healing in the region of myocardial infarction.

17. The observations on collateral circulation reported in this communication explain (1) the rarity of infarction in the right ventricle, (2) the more extensive amount of infarction in the subendocardial portion than in the subepicardial portion of the myocardium, and (3) the fact that infarcts are generally smaller than the mass of muscle supplied by occluded vessel.

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THE DIAGNOSIS OF MITRAL INSUFFICIENCY IN RHEUMATIC CHILDREN

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IT IS well known that many children with definite histories of chorea, rheumatic polyarthritis, or even carditis often recover completely. The only residuum frequently found in such individuals is an apical systolic murmur of varying intensity.

The exact significance of these murmurs in rheumatic children has been a controversial subject for many years. In 1923, the New York Heart Association suggested the following criteria for the diagnosis of mitral insufficiency: "The diagnosis of mitral insufficiency can be made in the presence of cardiac enlargement and of a typical murmur. The murmur alone is not sufficiently typical to establish the diagnosis, but with other valvular disease or in children with a history of one or more rheumatic manifestations, a typical murmur may be considered to indicate a mitral leak."[1] In subsequent editions of the criteria published by the New York Heart Association, it is stated unequivocally that without cardiac enlargement, deformity of the mitral valve should not be diagnosed, and no distinction is made between adults and children.[2]

The determination of minor degrees of cardiac enlargement, especially in children, even with the aid of roentgenologic or fluoroscopic examination, is often equivocal. Many experienced pediatricians, therefore, do not adhere strictly to the criteria. The diagnosis of mitral insufficiency, rather than that of potential and possible rheumatic heart disease, is frequently made because of the character of the apical systolic murmur. In patients with loud, blowing apical systolic murmurs, the physician often suspects that organic heart disease may be developing or may be present in spite of the lack of definite proof.

It was thought possible that the prognosis of patients in whom a diagnosis of mitral insufficiency was based on a loud, blowing, apical systolic murmur without demonstrable cardiac enlargement might differ from that of patients with soft, poorly transmitted apical systolic murmurs, classified as cases of potential and possible rheumatic heart disease. A comparison of the cardiac status of 144 cases of mitral insufficiency and 171 cases of potential and possible rheumatic heart disease, after an average follow-up period of eight years, was therefore undertaken.

From Irvington House, Irvington-on-Hudson, N. Y.
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MATERIAL

The material analyzed in this report was obtained from the records of patients who received convalescent care at Irvington House, a sanatorium for the care and study of children with rheumatic heart disease. Children, 6 to 15 years of age, with histories of one or more attacks of rheumatic fever or chorea were observed for various lengths of time ranging from two months to two years. Following discharge, each child was seen annually at the Irvington House After-Care Clinic where continuous records were maintained. The patients included in this study were followed for periods ranging from five to nineteen years, with an average of eight years.

DIAGNOSTIC CRITERIA

The records of 315 rheumatic patients discharged over a period of fifteen years (1927 to 1941) were selected for study. Group 1 consisted of 171 cases classified as having potential and possible rheumatic heart disease according to the criteria of the New York Heart Association.[2] These patients had soft, poorly transmitted, apical systolic murmurs and no evidence of cardiac enlargement.

Group 2 consisted of 144 cases diagnosed at the time of discharge as having mitral insufficiency. Eighty-three of these 144 children showed no cardiac enlargement by teleradiography. In the remaining sixty-one, teleroentgenograms were not available but on physical examination the heart was considered to be normal in size. The diagnosis in this group, therefore, was based entirely on the presence of a loud blowing systolic murmur, maximal at the apex, and well transmitted to the axilla. Children with systolic murmurs maximal at the base of the heart or those with musical systolic murmurs usually best heard in the third or fourth intercostal space near the sternum, regardless of intensity, were not included.

The composition of both groups according to sex, average age at onset of initial attack, average age of admission, and average number of years of follow-up is listed in Table I.

TABLE I. COMPOSITION OF GROUPS SELECTED FOR STUDY

DISCHARGE DIAGNOSIS	TOTAL NO. OF CASES	SEX		AVERAGE AGE, INITIAL ATTACK	AVERAGE AGE ON ADMISSION	AVERAGE NO. OF YEARS FOLLOWED
		MALE	FEMALE			
Potential and possible heart disease (Group 1)	171	79	92	8.3	11.6	8.2
Mitral insufficiency (Group 2)	144	52	92	7.4	11.3	8.1

RESULTS

Present Status.—The present cardiac status of these two groups is presented in Table II.

Table II shows that there has been no change in diagnosis in 149 (87 per cent) of the 171 patients classified on discharge as cases of potential and possible rheumatic heart disease (Group 1), after an average follow-up period of eight years. No deaths have occurred in this group and only twenty-two patients (13 per cent) have developed definite cardiac lesions.

In contrast, sixty-nine or 48 per cent of 144 patients diagnosed on discharge as cases of mitral insufficiency on the basis of the character of the apical systolic murmur, in the absence of demonstrable enlargement, have developed organic heart disease. Twenty of these sixty-nine children have died: in thirteen, death was due to rheumatic infection and in seven, to bacterial endocarditis.

TABLE II. CARDIAC STATUS AT TIME OF FINAL FOLLOW-UP

DISCHARGE DIAGNOSIS	TOTAL NO. OF CASES	POTENTIAL AND POSSIBLE HEART DISEASE	ORGANIC HEART DISEASE		
			LIVING	DEAD	TOTAL %
Potential and possible heart disease (Group 1)	171	149 (87%)	22 (13%)	0	13
Mitral insufficiency (Group 2)	144	75 (52%)	49 (34%)	20 (14%)	48

In view of the difference in the prognosis of these two groups of children, it was thought of interest to determine whether the presence of a loud, blowing, apical systolic murmur could be correlated with other evidence indicative of a severe rheumatic infection.

Type of Initial Attack.—The severity of the rheumatic infection in different individuals varies greatly. Most observers agree that the disease tends to be mild in patients whose only rheumatic manifestation is chorea (so-called "pure" choreas). On the other hand, carditis is generally accepted as an indication of a severe infection.

It was thought possible that the development of a loud, blowing apical systolic murmur might be related to the severity of the initial infection. The type of the initial attack in 144 cases diagnosed as having mitral insufficiency (Group 2) was therefore compared with that found in the 171 cases of potential and possible rheumatic heart disease (Group 1).

It is apparent (Table III) that there is no significant difference between the two groups in the incidence of chorea, chorea associated with rheumatic fever, or polyarthritis with or without carditis as the initial manifestation of the rheumatic infection. Chorea did not predominate in the cases of potential and possible rheumatic heart disease. Rheumatic fever was almost equally common in the two groups (Group 1: 79 per cent, and Group 2: 80 per cent).

TABLE III. TYPE OF INITIAL ATTACK

DISCHARGE DIAGNOSIS	TOTAL NUMBER OF CASES	UNCOMPLICATED CHOREA	CHOREA AND RHEUMATIC FEVER	RHEUMATIC FEVER
Potential and possible heart disease (Group 1)	171	21 (12%)	16 (9%)	134 (79%)
Mitral insufficiency (Group 2)	144	15 (11%)	13 (9%)	116 (80%)

Incidence of Multiple Attacks Prior to Admission.—The majority of patients who develop severe rheumatic heart disease usually have a history of multiple attacks, suggesting that they may be more susceptible to the disease than individuals who have a single attack or than those in whom the intervals between attacks are fairly long. The incidence of multiple attacks in the two groups was compared.

The data presented in Table IV show a marked difference in the incidence of multiple attacks in the potential and possible group as compared with the patients classified as having mitral insufficiency. Twice as many children in the latter group gave a history of repeated rheumatic recurrences. Rheumatic fever or rheumatic fever with chorea was more prevalent (89 per cent) in this group than in Group 1 (65 per cent). On the other hand, chorea was three times more common in Group 1 than in Group 2.

TABLE IV. INCIDENCE OF MULTIPLE ATTACKS PRIOR TO ADMISSION

DISCHARGE DIAGNOSIS	TOTAL NUMBER OF CASES	NO. OF CASES WITH MULTIPLE ATTACKS	TYPE OF ATTACK		
			CHOREA	CHOREA AND RH. FEVER	RH. FEVER
Potential and possible heart disease (Group 1)	171	52 (31%)	18 (35%)	2 (4%)	32 (61%)
Mitral insufficiency (Group 2)	144	92 (63%)	10 (11%)	10 (11%)	72 (78%)

The greater incidence of multiple attacks in children with loud, blowing apical systolic murmurs suggests that these patients were more susceptible to rheumatic infection than those with soft apical systolic murmurs. It is possible that these repeated attacks may have led to more marked valvular deformity which might account for the intensity of the apical murmur.

Incidence of Rheumatic Recurrences Following Discharge.—The incidence of rheumatic recurrences in the two groups following sanatorium care is presented in Table V.

Twelve (7 per cent) of the 171 patients in Group 1 had rheumatic recurrences following discharge. Nine of these twelve patients, in spite of the fact that they sustained multiple attacks, have shown no detectable evidence of cardiac involvement. Five had rheumatic fever as a recurrent manifestation and four chorea.

On the other hand, twenty-eight (19 per cent) of the 144 children in Group 2 had rheumatic recurrences. Following recurrences of rheumatic fever, twenty-two of these twenty-eight patients developed organic heart disease. In the remaining six, despite the fact that five had recurrences of rheumatic fever and one had chorea, the intensity of the murmur decreased and the diagnosis was changed from mitral insufficiency to potential and possible rheumatic heart disease.

TABLE V. INCIDENCE OF RHEUMATIC RECURRENCES FOLLOWING DISCHARGE

DISCHARGE DIAGNOSIS	CARDIAC STATUS AT TIME OF FINAL FOLLOW-UP	TOTAL NO. OF CASES	NO. WITH RECURRENCES FOLLOWING DISCHARGE	TYPE OF RECURRENCE		
				CHOREA	CHOREA AND RH. FEVER	RH. FEVER
Potential and possible heart disease (Group 1)	Potential and possible heart disease	149	9 (6%)	4	0	5
	Organic heart disease	22	3 (14%)	1	0	2
Mitral insufficiency (Group 2)	Potential and possible heart disease	75	6 (8%)	1	0	5
	Organic heart disease	69	22 (32%)	0	1	21

It may be seen from Tables IV and V that patients classified as cases of mitral insufficiency had more rheumatic episodes, both before and after sanatorium care, than did the patients included in the group of potential and possible rheumatic heart disease. The lower incidence of rheumatic recurrences following discharge in both groups is probably related to the fact that the incidence of rheumatic attacks tends to decrease as puberty is approached.

Analysis of Cardiac Lesions.—An analysis of the type of valvular deformity in patients who at the present time have definite evidence of organic heart disease is presented in Table VI.

Table VI shows that, although in contrast to Group 2 relatively few patients in Group 1 developed organic heart disease, there was no significant difference between the two groups in the type of cardiac lesions.

Analysis of Deaths.—There were no deaths in the group of potential and possible heart disease. Of the 144 patients classified as mitral insufficiency, thirteen have died as a result of their rheumatic infection. The average age of onset of the initial attack in the group that died (6.2 years) was slightly lower than that for the entire group (7.8 years). Four of the deaths were the result of

rheumatic myocarditis and occurred, on the average, three years following the initial attack. In the remaining nine patients, death was due to congestive heart failure. In these children, the average interval between the onset of the rheumatic infection and death was 11.7 years.

TABLE VI. ANALYSIS OF CARDIAC LESONS

DISCHARGE DIAGNOSIS	TOTAL NO. OF CASES	NO. WITH ORGANIC HEART DISEASE	MI	MI, MS	MI, MS, AI	AI
Potential and possible heart disease (Group 1)	171	22 (13%)	0	15 (68%)	1 (4.5%)	6 (27.5%)
Mitral insufficiency (Group 2)	144	69 (48%)	5 (7%)*	40 (58%)	13 (19%)	11 (16%)

*These five patients died of bacterial endocarditis.

It is of interest that ten of these thirteen children had more numerous and more severe rheumatic attacks prior to admission than any of the other children, yet at the time of observation, the only physical finding was a loud blowing apical systolic murmur. Following discharge, the incidence of rheumatic recurrences was higher in the thirteen children who died than in the other patients classified as cases of mitral insufficiency who survived.

In addition to the thirteen patients who died of their rheumatic infection, seven (4.8 per cent) children in Group 2 succumbed to bacterial endocarditis, whereas none of the patients in Group 1 developed this infection.

DISCUSSION

The frequency with which apical systolic murmurs are found in normal individuals has made physicians skeptical as to their significance in rheumatic subjects. Stethographic records show that such murmurs occur in 90 per cent of normal children.[3] As methods for determining cardiac enlargement by roentgenologic and fluoroscopic examination improved, it was thought that these would serve as objective means of evaluating apical systolic murmurs. According to the Criteria of the New York Heart Association these murmurs should be considered indicative of organic heart disease only if they are accompanied by cardiac enlargement.[2]

Unfortunately, however, the determination of minor degrees of enlargement by roentgenography or fluoroscopy, especially in children, is extremely difficult. Although there is always a danger that the diagnosis of mitral insufficiency may be made on the basis of a functional murmur by the inexperienced physician, cardiologists will usually agree more readily on what constitutes a significant apical systolic murmur than on what constitutes slight cardiac enlargement. Moreover, different observers vary greatly in their criteria for diagnosing minimal

enlargement by roentgenologic or fluoroscopic examination, and even the same observer often finds it difficult to be consistent. The variations in the size of the normal heart must be constantly borne in mind. The degree of enlargement sufficient to be detectable in an individual with a vertical heart is much greater than in one with a heart of the horizontal type. Furthermore, in very young children the heart is often globular and appears large in proportion to the size of the chest. As the child grows, a normal relationship between heart size and the chest becomes apparent, so that what might have been considered enlargement at the age of 3 or 4 years was probably only a relative increase in size.

In adults, longstanding valvular damage often causes hypertrophy of the cardiac musculature which, when followed by secondary dilatation, results in demonstrable cardiac enlargement. In children, on the other hand, the chief cause of unequivocal cardiac enlargement is dilatation due to acute infection or chronic myocarditis. Hypertrophy takes several years to develop and is uncommon in childhood. In contrast to adults, therefore, cardiac enlargement in children is not necessarily proof of valvular deformity.

Although valvular incompetency often causes cardiac enlargement in older individuals, the intensity of the apical systolic murmur has been found to be a valuable prognostic sign in adults in whom enlargement is equivocal or absent. In 1927, White,[4] in a follow-up study of 1,050 unselected private patients, found that there was a direct relationship between the loudness of the apical systolic murmur and the development of organic heart disease. In 1943, this observer, in association with Baker and Sprague, published further data corroborating this opinion.[5] In 1933, Freeman and Levine, studying a group of 1,000 "noncardiac" individuals, were the first to grade the intensity of apical systolic murmurs. These authors concluded, as had White, that irrespective of etiology, the more intense the murmur the more serious the prognosis was likely to be.[6,7]

In children, on the other hand, the importance of the intensity of the murmur has not been emphasized probably because it was thought that loudness might be related to the proximity of the heart to the chest wall. Better transmission, however, does not adequately explain the marked variations in the intensity of murmurs heard in children of the same body build.

In 1938, Boone and Levine[8] published a study on the prognosis in potential rheumatic heart disease and rheumatic mitral insufficiency based on the analysis of 225 patients ranging in age from 12 to 20 years, with an average age of 13.8 years. None of these patients showed evidence of cardiac enlargement. They were divided into two groups solely on the basis of the intensity of the apical systolic murmurs. One hundred sixty-six patients classified as cases of potential heart disease had soft, poorly transmitted murmurs (Grade 1) and fifty-nine patients, classified as cases of mitral insufficiency had louder murmurs (Grade 2 or more). After a follow-up period of 9.6 years, these authors found a striking difference in the incidence of organic heart disease in the two groups; only 4.8 per cent of 166 cases of potential heart disease had developed mitral stenosis, aortic insufficiency, or both, as compared with 42 per cent of the fifty-nine cases diagnosed as having mitral insufficiency.

The data reported in this paper are in accord with the findings of Boone and Levine. The evidence presented by these authors, as well as our observations, indicates that the intensity of apical systolic murmurs, even in the absence of cardiac enlargement, is a valuable prognostic sign. The fact that children with loud murmurs in our series had had more rheumatic attacks prior to the period of observation suggests that organic damage may have been present at the time of the initial examination. The absence of concomitant demonstrable enlargement merely indicates that myocardial involvement of a detectable degree had not developed.

Further evidence that the intensity of the apical systolic murmur has prognostic significance in known rheumatic subjects is our finding that patients with this type of murmur had more frequent rheumatic attacks during the follow-up period than did children with soft, poorly transmitted apical murmurs. All of the children in the latter group survived, whereas thirteen of the 144 patients classified as cases of mitral insufficiency died as a result of their rheumatic infection. In addition, seven children in the latter group died of bacterial endocarditis. In two of these seven individuals, mitral stenosis had developed. In the remaining five, the original diagnosis of mitral insufficiency had not changed at the time this infection occurred, indicating that deformity of the mitral valve was present.

It is generally agreed that the prognosis in rheumatic children with well-marked cardiac enlargement is usually worse than that in children with identical lesions and minimal enlargement or none. In patients, therefore, in whom a loud blowing apical systolic murmur is accompanied by cardiac dilatation, the probability of further cardiac damage is greater than in those in whom the myocardium appears normal.

In view of the difficulty of detecting minor degrees of cardiac enlargement, our findings indicate that the diagnosis of mitral insufficiency based on the intensity of the apical systolic murmur, in the absence of demonstrable cardiac enlargement, is justified in children. Susceptible individuals are most vulnerable to rheumatic fever during childhood. After puberty the incidence of rheumatic recurrences declines and the danger of progressive cardiac damage becomes less. It is, therefore, important to differentiate children in whom a more serious prognosis is anticipated from those who may be expected to run a milder course. The observations of Boone and Levine, as well as ours, suggest that the intensity of the apical systolic murmur has prognostic significance. In children the diagnosis of mitral insufficiency, made on the basis of the type of apical systolic murmur, is a means of indicating the severity of the rheumatic infection.

CONCLUSIONS

1. The prognosis of 144 rheumatic children, with a diagnosis of mitral insufficiency based on a loud blowing apical systolic murmur in the absence of cardiac enlargement, was compared with the prognosis of 171 children classified as having potential and possible rheumatic heart disease after an average follow-up period of eight years.

2. Of the 144 cases of mitral insufficiency, sixty-nine patients (48 per cent) have developed organic heart disease. Of these, thirteen died as a result of their rheumatic infection and seven succumbed to bacterial endocarditis. Ninety-two (63 per cent) of these 144 cases had a history of multiple attacks prior to the period of observation and twenty-eight (19 per cent) had rheumatic recurrences following sanatorium care.

3. Of the 171 cases of potential and possible rheumatic heart disease, twenty-two patients (13 per cent) developed evidence of organic heart disease. None of the children in this group died. Fifty-two (31 per cent) of the 171 cases had a history of multiple attacks prior to the period of observation and twelve (seven per cent) had rheumatic recurrences following sanatorial care.

4. The striking difference between the two groups in the progression of the disease and the mortality rate indicates that the intensity of the murmur is of prognostic significance.

5. The diagnosis of mitral insufficiency, based on a loud blowing apical systolic murmur, is justified in children, even in the absence of demonstrable cardiac enlargement.

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THE RELATION OF UNIPOLAR LIMB LEADS TO PRECORDIAL AND ESOPHAGEAL LEADS

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THE utilization of a central terminal of nearly zero potential as an indifferent electrode enabled Wilson and associates[1-4] to introduce a new type of lead that could be considered unipolar in the sense that the tracings obtained represent largely, but not quite exclusively, the potential variations of the exploring electrode. With these galvanometric connections they obtained unipolar semidirect leads in which the exploring electrode was applied to the precordium or esophagus and analogous unipolar limb leads (V_R, V_L, and V_F) in which the exploring electrode was applied to one extremity and the indifferent electrode to all three.

Wilson and associates demonstrated that the QRS-T complex of a given precordial lead in dogs was comparable in configuration to that obtained through a direct lead from the underlying epicardium. Brown[5] demonstrated that the pattern obtained through an esophageal lead in dogs corresponds closely to that recorded through a direct lead applied to the underlying posterior wall of the heart. Thus, a precordial lead reflects the potential variations of the epicardial surface of the subjacent anterior wall of the heart and an esophageal lead reflects the potential variations of the epicardial surface of the subjacent posterior wall.

Wilson and associates noted that the QRS-T complex of a given unipolar limb lead simulated that recorded from the trunk at the junction of the respective extremity and frequently, but not invariably, resembled the QRS-T complex obtained in one of the customary precordial leads. The relationship of limb to multiple precordial leads varied in different individuals, depending upon the position of the heart in the chest. They described five cardiac positions, ranging from vertical, manifested by a pattern in Lead V_L resembling that of V_1 or V_2 and a pattern in Lead V_F like that of V_5 and V_6, to horizontal, characterized by a QRS complex in Lead V_L like that of V_5 and V_6 and a QRS in Lead V_F like that of V_1 or V_2. They also included a sixth category, an indeterminate position, in which there was no obvious relationship between the ventricular complexes of limb and precordial leads.

Wolferth and associates[6-8] further investigated transmission of potentials from precordium to the extremities by means of successive tracings from inter-

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mediate points. In this manner, they generally succeeded in demonstrating a pathway extending from a point near the heart into an extremity, along which the QRS-T complex remained fairly uniform in shape. The pathway into the left arm most commonly originated from the C_5 position, sometimes from points higher and more medial; that into the right arm usually started from the C_1 position; that into the left leg traversed the diaphragm, stomach, intestines, and anterior and posterior surfaces of the trunk below the umbilicus. From these studies it would appear that the potential variations of a given extremity are dominated by those of the epicardial surface which faces toward that extremity. This is, in turn, dependent upon the position of the heart in the chest.

Goldberger[9] modified the Wilson procedure in obtaining unipolar limb leads by removing the connection of the central terminal from the limb to which the exploring electrode was attached. Tracings obtained in this manner with 5,000 ohm resistances in each of the connections of the indifferent electrode are identical in contour, but 50 per cent greater in voltage, than those recorded by the Wilson technique.[9,10] Goldberger has described the commoner patterns in his augmented unipolar limb leads aV_R, aV_L and aV_F[11,12] and has commented upon their relations to the patterns in semidirect precordial and esophageal leads.[13-15]

METHODS OF STUDY

To further elucidate the relationships between semidirect and unipolar extremity leads, a study was undertaken of a group of subjects whose hearts were considered normal by clinical and roentgenologic examination. In addition to the customary Wilson precordial and esophageal leads and the Goldberger extremity leads, records were obtained from a large number of points on the anterior and posterior aspect of the trunk intervening between the projected cardiac borders and each of the three extremities. Esophageal leads were usually recorded at half-normal galvanometric sensitivity, Wilson precordial leads were obtained in the customary fashion, but all other leads from the trunk and extremities were taken by the Goldberger procedure, that is, by breaking the connection of the central terminal to the extremity which the exploring electrode was approaching. This exaggerated the deflections in comparison with leads from the esophagus and from precordial points C_1 through C_6 but made them comparable to those recorded in Leads aV_R, aV_L, and aV_F. Each of the Goldberger extremity leads was compared with the records from the esophagus and trunk in order to locate its counterpart in the semidirect leads and to map out the intervening pathway along which the QRS-T maintained a uniform shape resembling both the semidirect and extremity leads at either terminus. The position of the exploring electrode in each record along this pathway was charted with respect to anatomic landmarks.

FINDINGS

The findings in five subjects were selected as collectively illustrative of the common variations in the relation of semidirect to unipolar limb leads. The

results are presented graphically in the form of diagrams, including a tracing from each of the three extremities along with its counterpart in a semidirect lead and indicating the approximate position of the heart in the chest and the anatomic location of the exploring electrode for each tracing represented. In some of the illustrations, the tracings obtained along the intervening pathway between the semidirect and extremity leads are included.

In Fig. 1,*a*, Wilson precordial and Goldberger extremity leads obtained on the first subject in the recumbent position during expiration are arranged in proximity to the anatomic position of the exploring electrode. Tracings obtained from representative intervening Points *A*, *C*, and *D* between the sites for Leads V_5 and aV_L are reproduced in the first row. Records from representative points *F*, *G*, and *H* on the lower abdomen are arranged along with Leads E_{55}* and aV_F in the second row. Representative leads from Points *J*, *K*, and *L* across the right anterior chest into the right arm are reproduced in the third row. Points *A*, *C*, *D*, *F*, *G*, *H*, *J*, *K*, and *L* are indicated in Fig. 1,*a* but, to avoid excessive lettering, are labelled only in Fig. 1,*b*.

A study of the tracings in the first row reveals a pathway extending from the position of Lead V_5 through Points *A*, *C*, and *D* in the anterior axillary line to the left arm, along which the QRS-T maintained a fairly constant shape, merely decreasing in voltage with increasing distance from the heart. Since the predominant influence on the potential variations of an extremity is derived from the nearest epicardial surface, the diagram is constructed to conform with the electrocardiographic findings and depicts the anterolateral aspect of the left ventricle facing both toward the position of Lead V_5 and the left arm.

The tracings obtained at Points *F*, *G*, and *H*, reproduced in the second row, are representative of numerous additional records from the anterior, left lateral, and posterior aspects of the trunk below the umbilicus. The QRS-T of Lead aV_F is almost identical with that obtained at Points *F*, *G*, and *H* and resembles closely that registered through an esophageal lead at the ventricular level (E_{55}).* This common pattern represents a transmission of potential variations from the inferior surface of the heart to the diaphragm and thence to all parts of the body below. The small slurred R wave, relatively deep S, and upright T of Lead aV_F, leads from Points *F*, *G*, and *H*, and Lead E_{55} correspond in general shape to the average of the tracings in Leads V_1, V_2, and V_3. Since the potential variations of the anterior aspect of the right ventricle have the dominant influence on the pattern in Leads V_1, V_2, and V_3 in this subject, the potential variations of the inferior surface of the right ventricle would appear to be chiefly responsible for the corresponding pattern obtained from points below the umbilicus and those of the posterior surface of the right ventricle are the presumptive source of the pattern recorded from the lower esophagus. Thus, the right ventricle comprises the diaphragmatic surface of the heart. The transmission of the potential variations of the anterolateral aspect of the left ventricle to the left arm and those of the right ventricle to the left leg indicates that the heart is in horizontal position.

*Esophageal lead with electrode 55 cm. distal to the nose and, therefore, over the ventricle.

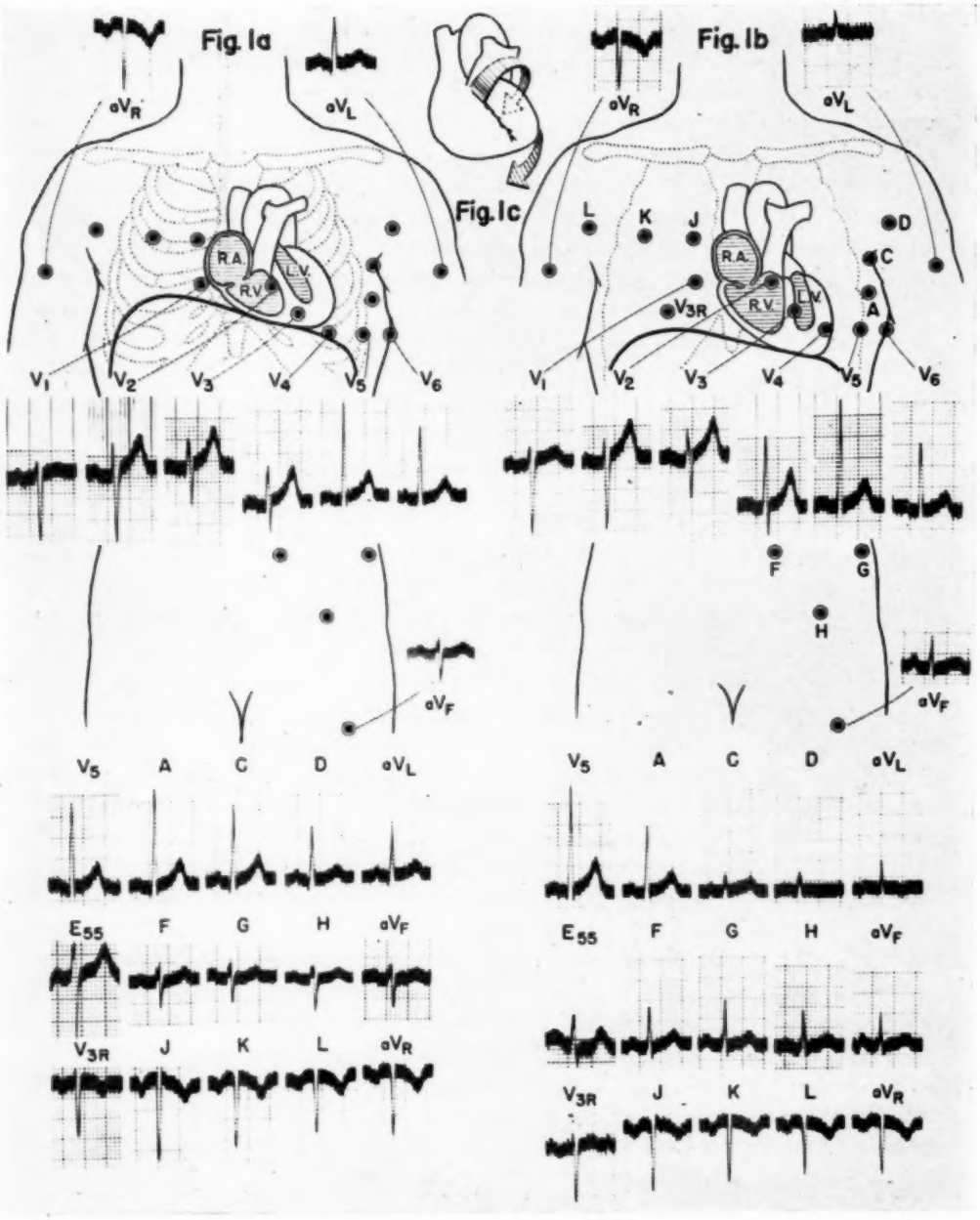

Fig. 1.—Relation of unipolar limb leads to leads from the trunk and esophagus in the first subject. 1, *a*, Schematic diagram of heart during forced expiration, illustrating findings in horizontal position. 1, *b*, Diagram of heart during full inspiration, illustrating findings in intermediate position. 1, *c*, Direction of cardiac rotation during inspiration.

The QRS-T complex of Lead aV_R has no exact counterpart among any of the six customary precordial leads. The record at the position of Lead V_1 is most nearly like that obtained from the right arm, but possesses a small initial R wave which is lacking in Lead aV_R and also differs in the direction of the T wave. Lead V_{3R} displays an RS complex like that of V_1, but shows an inverted T wave more like that of Lead aV_R. The small initial R wave of Leads V_1 and V_{3R} resembles that recorded either through a direct lead from the epicardium of the anterolateral aspect of the right ventricular wall of dogs[16] or human subjects[17] or through insertion of an electrode directly into the right ventricular cavity of dogs[16] and human subjects.[18] The presence of a minute initial R in tracings from the right ventricular cavity may be due either to earlier onset of activation of the left side of the septum[19] or to greater magnitude of electrical forces developed in the left than in the right half of the septum. The disappearance of the initial R wave as the electrode is moved from the position of Lead V_1 in the fourth intercostal space at the right sternal border to Point *J* in the second intercostal space at the right sternal border is analagous to that which has been demonstrated by retracting the electrode from the right ventricular cavity into the upper portion of the right atrium or superior vena cava.[18] The disappearance of the minute initial R in shifting the electrode from the right ventricular cavity to the superior vena cava is probably due partly to loss of positive potential with increasing distance and partly to the opposing effects of the negative potentials of the left ventricular cavity transmitted through the mitral orifice and the interatrial septum.

From the similarity of the records from Points *J*, *K*, and *L* and Lead aV_R, it would appear that the QS pattern of Lead aV_R is transmitted along this pathway. However, this does not constitute the only pathway to the right arm. The QRS-T recorded through esophageal leads at the atrial level is similar to that at Point *J* and Lead aV_R except for the presence of a small late R wave. The upper esophageal pattern was transmitted to the right side of the back and thence to the right arm as illustrated in Fig. 2, which shows a series of tracings obtained as the electrode was moved across the right scapula (Points *M*, *N*, and *O*). The minute terminal R wave evident in leads near the midline disappeared as the electrode was moved laterally into the shoulder and was absent from Lead aV_R. Thus, the QS complex and inverted T wave of Lead aV_R represented cavity potentials resembling those which can be recorded over the right atrium anteriorly or from the esophagus behind the left atrium. Hence in the cross-sectional diagram of Fig. 2, the right atrium is depicted as facing toward the right anterolateral chest wall and right arm, the left atrium toward the right posterior chest wall and right arm.

The tracings in Fig. 1,*b* were taken during full inspiration on the same subject and from the same points as those in Fig. 1,*a*. This was accomplished as follows: A record was first made from a given point during expiration and then, with the electrode maintained at the same location, a second tracing was taken during full inspiration. There was a close correspondence of the QRS obtained in the precordial leads during the two phases of respiration, except at the pre-

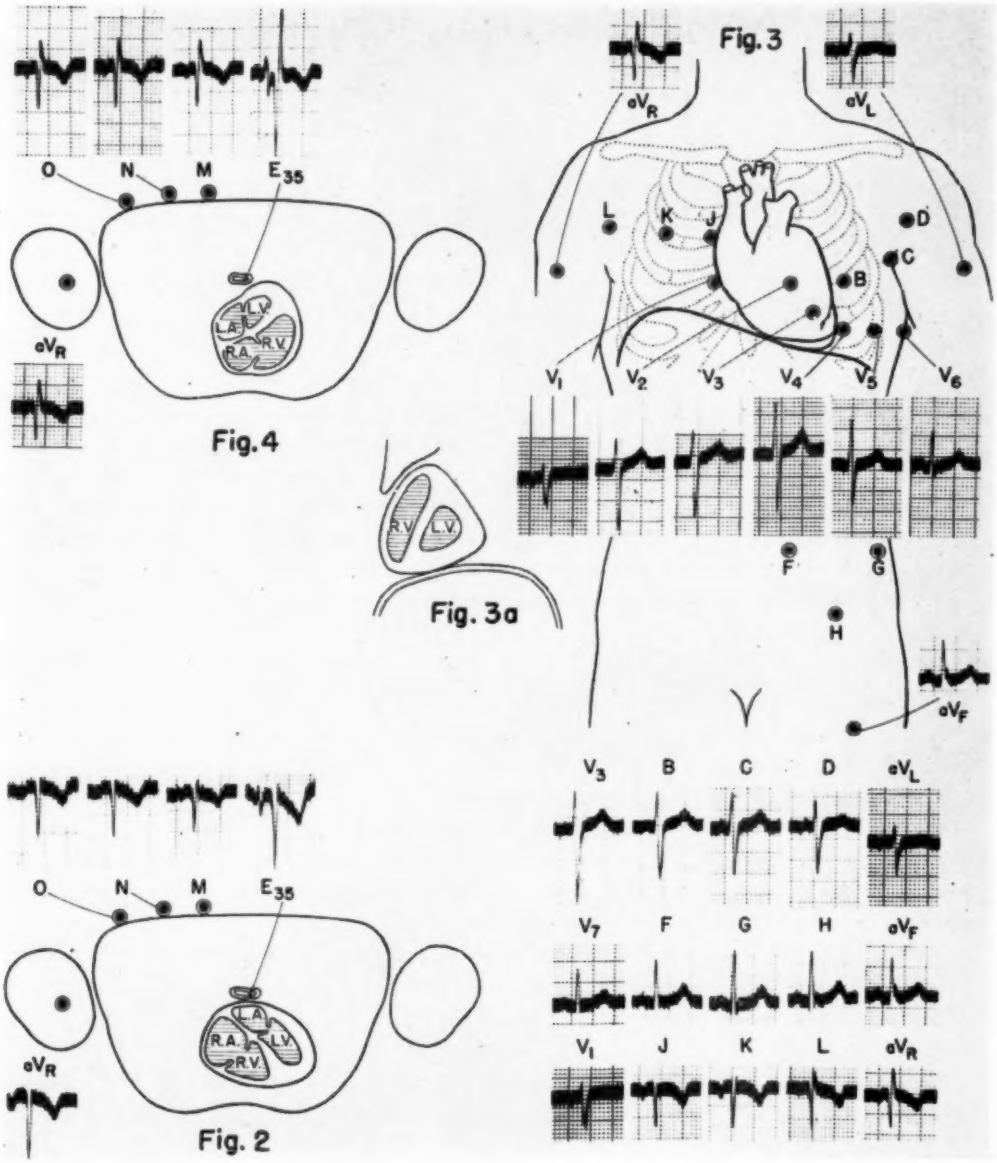

Fig. 2.—Cross-sectional diagram to illustrate relation of Lead aVR to leads from the back and esophagus and to the cardiac chambers in the first subject.

Fig. 3.—Relation of unipolar limb leads to leads from the trunk in the second subject, exemplifying the findings in vertical position of the heart. 3, *a*, Schematic sagittal section, to show relation of left ventricle to diaphragm in the second subject.

Fig. 4. Cross-sectional diagram, to show relation of Lead aVR to leads from the back and esophagus and to the cardiac chambers in the second subject, exemplifying the findings in backward rotation of the left apex.

cordial position of Lead V_4. The relatively small, slurred, nearly equiphasic QRS complex obtained at position C_4 during expiration suggested that the electrode lay over the interventricular septum, whereas the tall R and relatively small S registered from the same point during full inspiration indicated that the heart had shifted sufficiently so that the left ventricle was beneath the electrode. The change in the direction of the T wave in Lead V_{3R} and change in amplitude of the T wave in V_1 is merely illustrative of the normal variability of the T wave in these leads. Deep inspiration did not significantly alter the pattern in Lead aV_R or the pathway for the transmission of cavity potentials from the second intercostal space at the right sternal border to the right arm.

In contrast to the relatively minor changes in the precordial leads and in Lead aV_R, full inspiration caused striking changes in the QRS pattern in Leads aV_L and aV_F. During full inspiration, the R wave in Lead aV_L underwent a 50 per cent decrease in voltage and the T wave became flattened. However, the general contour of the QRS in this lead still corresponded more closely to that in Leads V_5 and V_6 than the other precordial leads, suggesting that the potential variations of the anterolateral aspect of the left ventricle were still being transmitted to the left arm. A study of the intermediate tracings taken between the position of Lead V_5 and the left arm and reproduced in the first row of Fig. 1,*b* reveals that the major decrement in voltage occurred between position of Lead V_5 and Point *C*. This is probably due partly to a clockwise rotation of the heart on its anteroposterior and longitudinal axes, as indicated in the insert, Fig. 1,*c*, and partly to alteration in electrical conductivity by full inflation of the lung.

The marked shift in the electrical position of the heart is better shown by a comparative study of leads from the lower esophagus, left leg, and lower abdomen of Fig. 1,*a* and *b*. The ventricular complex registered from all of these points during full inspiration consisted of a tall R, minute S, and upright T, resembling that of left ventricular Lead V_5, whereas the QRS-T during expiration consisted of a small R and relatively deep S, resembling that of right ventricular Leads V_1, V_2, and V_3. This indicates that the heart shifted sufficiently with the descent of the diaphragm so that the inferior surface of the left ventricle came in contact with the diaphragm and lower esophagus, in place of the right ventricle. When the potential variations of the epicardial surface of the left ventricle are transmitted to both the left arm and left leg, so that the QRS-T in Leads aV_L and aV_F resemble one another and correspond, in general contour, to precordial Leads V_5 or V_6, the heart is in intermediate position.

The inspiratory shift in the relation of the heart to left arm, diaphragm, and left leg is accomplished through clockwise rotation on its anteroposterior axis, so as to bring the apex downward and medially as indicated by the lower arrow of the insert, Fig. 1,*c* and through simultaneous rotation of the heart on its longitudinal axis in the direction of the upper arrow (clockwise, as viewed from below), so as to bring the inferior wall of the left ventricle into closer apposition with the diaphragm and lower esophagus. The clockwise rotation on the anteroposterior axis during the inspiratory descent of the diaphragm is also

represented diagrammatically in Fig. 1,*a* and *b*. In the expiratory position depicted in Fig. 1,*a*, the right ventricle rested on the diaphragm. In shifting to the inspiratory position in Fig. 1,*b* sufficient rotation on an axis passing from sternum to vertebrae through the great vessels has occurred in the direction of the arrow in Fig. 1,*c* to bring the left ventricle into contact with the diaphragm. The rotation about the longitudinal axis may be better appreciated by a study of Fig. 2 in conjunction with Fig. 4, which are cross-sectional diagrams representing the position of the heart in the first and second subjects, respectively. During inspiration, rotation occurred about a longitudinal axis passing through the center of the septum in a direction from the position depicted in Fig. 2 toward the position shown in Fig. 4. However, the degree of rotation between the expiratory and inspiratory positions in the first subject was not nearly as great as the difference in the two subjects as depicted in their respective cross-sectional diagrams. The rotation from the position in Fig. 2 to that in Fig. 4 appears counterclockwise in these cross-sectional diagrams, which are drawn as viewed from above. The same direction of rotation would appear clockwise if viewed from below, as may be appreciated by holding the side of the page containing Figs. 2 and 4 against a light and viewing the two diagrams from the reverse (that is, the under) side of the page. Since it is customary to designate rotation about a longitudinal axis by the direction taken as viewed from below (that is, from the cardiac apex), the rotation which would have occurred from the position in Fig. 2 to that in Fig. 4 is designated as clockwise.

The tracings in Figs. 3 and 4 were obtained on the second subject, whose external build appeared comparable to that of the first. The records were taken from points corresponding as closely as possible to those in the first subject. The pattern in Leads V_1 and V_2 of Fig. 3 simulated that in the same leads of Fig. 1,*a* and *b*, and the pattern in Leads V_6 and V_7 was comparable to that in Leads V_5 and V_6 of the former subject. Intermediate precordial leads differed considerably due to the fact that the transition was more gradual and extended further to the left in this subject.

Although leads at corresponding sides of the precordium were comparable in the two individuals, the unipolar limb leads displayed a striking contrast. The relatively small R and deep S recorded in Lead aV_L resembled the pattern in Leads V_2 and V_3 and differed considerably from that in Leads V_5, V_6, and V_7. The fact that the potential variations of the portion of the heart which dominated the record in Lead V_3 were transmitted into the left arm was borne out by attempts to trace the pathway from the left side of the heart into the left arm. In this case, the pattern found in Lead aV_L was maintained along a pathway running from the position of Lead V_3 through Points *B*, *C*, and *D*, whereas the pattern registered in Lead aV_L of Fig. 1,*a* was transmitted from Position C_5 along a pathway through Points *A*, *C*, and *D*. The close resemblance of the QRS-T in Leads aV_L and V_3 of this case to that in right ventricular Leads V_2 and V_1 indicates a marked clockwise rotation of the heart on an anteroposterior and longitudinal axis sufficient to permit the transmission of potential variations of the epicardial surface of the right ventricle to the left arm. The relationship

of the anterosuperior portion of the right ventricle to the left arm is illustrated diagrammatically by anteroposterior view in Fig. 3 and by cross section in Fig. 4.

The R and T waves in leads from the left leg and lower abdomen were almost identical with those in Leads V_6 and V_7. In some of these leads (V_6 and Point *G*) a small S wave was visible, whereas in other leads (aV_F and Point *H*) the same event gave rise to a small notch at the end of the R wave. The similarity to Leads V_6 and V_7 indicates that leads from the lower abdomen and left leg reflected the potential variations of the epicardial surface of the left ventricle. This occurs when the portion of the heart in contact with the diaphragm consists of left ventricle, as illustrated by insert Fig. 3,*a*. Since tracings from the lower esophagus in this case also resembled Leads V_6 and V_7, the potential variations of the posterior aspect of the left ventricle were transmitted to the esophagus. When the left ventricle is directed posteriorly and inferiorly, facing toward the lower esophagus and left leg, and the right ventricle lies anteriorly and superiorly, facing toward the left arm, the heart is in vertical position.

The QRS of Lead aV_R of this subject displayed a prominent late R wave and thus differed decisively from the QS pattern found in the tracings of the first subject. The fact that the late R wave of Lead aV_R was not present in Leads V_1, V_{3R}, or in other leads from the right anterior chest wall (that is, at Points *J* and *K*) would indicate that it was not transmitted from the portion of the right ventricle or atrium forming the anterolateral margin of the heart. Thus when successive tracings were taken in the second or third intercostal space, starting at the right sternal border and progressing toward the right arm, a distinct late R wave was first obtained when the junction of the trunk and arm was reached (Point *L*). This R wave increased in amplitude when the exploring electrode was moved farther into the arm.

The origin of the late R wave of Lead aV_R is evident through a study of esophageal leads at the atrial level, together with leads taken across the right scapula and reproduced in Fig. 4. The intrinsicoid deflection in the P wave indicates that the esophageal electrode lay behind the left atrium. The resemblance of the P wave to that in the esophageal lead of the first subject (Fig. 2) would suggest that the electrode was in comparable position. Nevertheless, there is a striking difference in the amplitude of the R waves in the esophageal leads of the two subjects. The Q-R relationships were duplicated in leads taken across the right scapula (as exemplified by the records at Points *M*, *N*, *O*) and also in Lead aV_R. Thus, the Q-R pattern in Lead aV_R was apparently transmitted from the posterior aspect of the heart through the back to the right arm. The late R wave recorded in esophageal leads at the auricular level was derived from the posterobasal portion of the left ventricle near the auricular margin, which is the last portion of the heart to become activated.

The maintenance of the late R pattern across the right side of the back and into the right arm indicates that a part of the posterobasal portion of the left ventricle faced toward the right side of the back and right arm. This occurs when the apex is rotated backward on a transverse axis passing through the axillae and great vessels coupled with sufficient clockwise rotation to tilt

the posterobasal aspect of the left ventricle upward and to the right, as represented diagrammatically in Figs. 3,*a* and 4. Thus, backward rotation of the apex tends to favor transmission of the potential variations of the epicardial surface of the posterobasal aspect of the left ventricle and adjacent atrium upward. Whether these potentials are referred to the right arm, to the left arm, or to both upper extremities appears to depend upon the degree of rotation about the other two axes. On the contrary, the more common forward rotation of the apex displayed by the first subject tilts the posterobasal surface of the left ventricle downward away from the upper extremities, so that the two atria face toward the right arm (Fig. 2), resulting in a downwardly directed QRS in Lead aV_R with or without a rudimentary late R wave.

If sufficient precordial and esophageal leads are taken, a semidirect lead can be found in which the QRS-T pattern resembles that of a unipolar limb lead. The potential variations of an extremity are governed principally by those of the surface of the heart which faces toward the limb and thus depend upon the position of the heart in the chest. Transmission of patterns from points near the surface of the heart to the extremity has been illustrated for horizontal, intermediate, and vertical positions of the heart. The relationship of semidirect precordial or esophageal leads to unipolar limb leads in other positions of the heart will be shown in Figs. 5, 6, 7, 8, 9, and 10.

The tracings obtained through a further study of the first subject are reproduced in Fig. 5. The relationship of Lead aV_R to a lead from the esophagus at the auricular level is similar to that depicted in Fig. 2 and the relationship of Lead aV_L to Lead V_6 is similar to that illustrated in Fig. 1,*a*. The essential difference from Fig. 1,*a* and Fig. 1,*b* lies in the tracings from the lower esophagus and from Lead aV_F. Leads E_{55} and aV_F of Fig. 5 were obtained about midway between expiration and full inspiration and display small slurred R and S deflections of approximately equal amplitude. Leads E_{55} and aV_F of Fig. 1,*a*, which were obtained on the same subject during expiration, show a relatively small R and deep S, whereas the corresponding leads taken during full inspiration and reproduced in Fig. 1,*b* show a relatively tall R and small S. As previously pointed out, the QRS of Leads E_{55} and aV_F of Fig. 1,*a* is comparable to that obtained through precordial leads over the right ventricle, whereas the QRS of Leads E_{55} and aV_F of Fig. 1,*b* is comparable to that obtained through precordial leads over the left ventricle. The small slurred equiphasic RS complex of Leads E_{55} and aV_F of Fig. 5 is comparable to that obtained through precordial leads at the transitional zone between the right and left ventricles (Lead V_4 of Fig. 1,*a*). It would thus appear that at the midpoint of the respiratory rotation of the heart of Subject 1, the potential variations of the posterior inferior aspects of the interventricular septum are referred to the lower esophagus, diaphragm, and left leg, giving rise to the small diphasic RS complex of Leads E_{55} and aV_F of Fig. 5. An attempt has been made to illustrate the anatomic relationships in Fig. 5. When the pattern in Lead aV_L simulates that of left ventricular Leads V_5 and V_6 and that in Lead aV_F consists of a diphasic or multiphasic complex of low voltage resembling that recorded from points near the interventricular septum, the

heart is in semihorizontal position. This position is about midway between the horizontal, depicted in Fig. 1,*a*, and the intermediate position, shown in Fig. 1,*b*.

The unipolar limb leads and selected precordial leads reproduced in Fig. 6 were obtained upon a third subject with a normal heart. Lead aV_R exhibits a QS complex and an inverted T wave, which is almost identical with that in Lead V_{3R}. The pattern in both leads suggests that the electrode faced the right atrium, as illustrated in the diagrams, thereby recording the potential variations of the

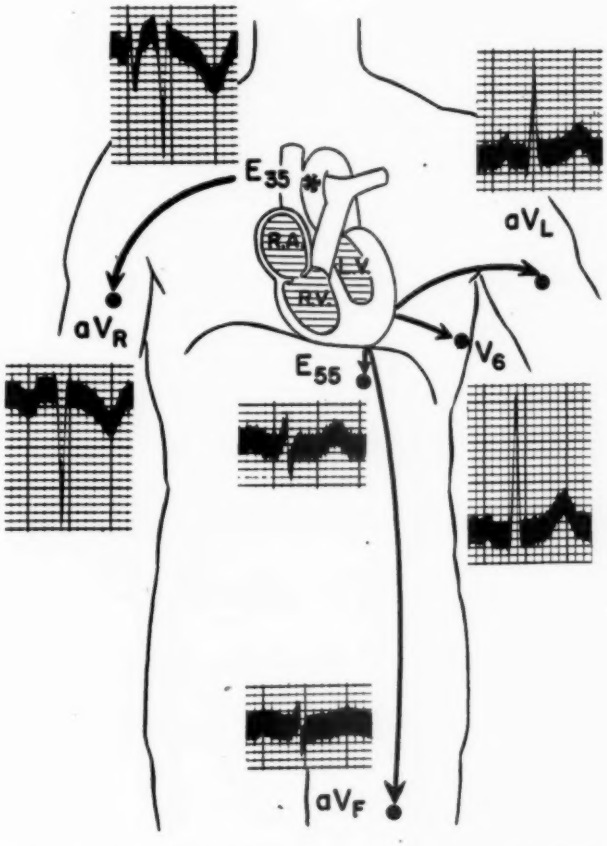

Fig. 5.—Relation of unipolar limb leads to precordial and esophageal leads obtained midway between expiration and inspiration in the first subject, exemplifying the findings in semihorizontal position of the heart.

ventricular cavities. Lead aV_F is an almost perfect replica of Lead V_5, indicating that the potential variations of the left ventricle were transmitted to the diaphragm and thence to the left leg in a manner similar to that shown in Fig. 3. The QRS of Lead aV_L consists of a small R and a slightly larger, splintered S wave and thus resembles the small R and larger, splintered S wave recorded in Lead V_3. The QRS of Lead aV_L is low in voltage in comparison to other limb leads and the QRS of Lead V_3 is less than one-half the voltage of that in other pre-

cordial leads, such as V_{3R} and V_5. The low voltage and coarse splintering of the QRS in Lead V_3 indicates that the lead was at the transitional zone, the electrode lying near the interventricular septum. The similar pattern in Lead aV_L suggests that the interventricular septum faced toward the left arm, as illustrated in the accompanying cross-sectional diagram.

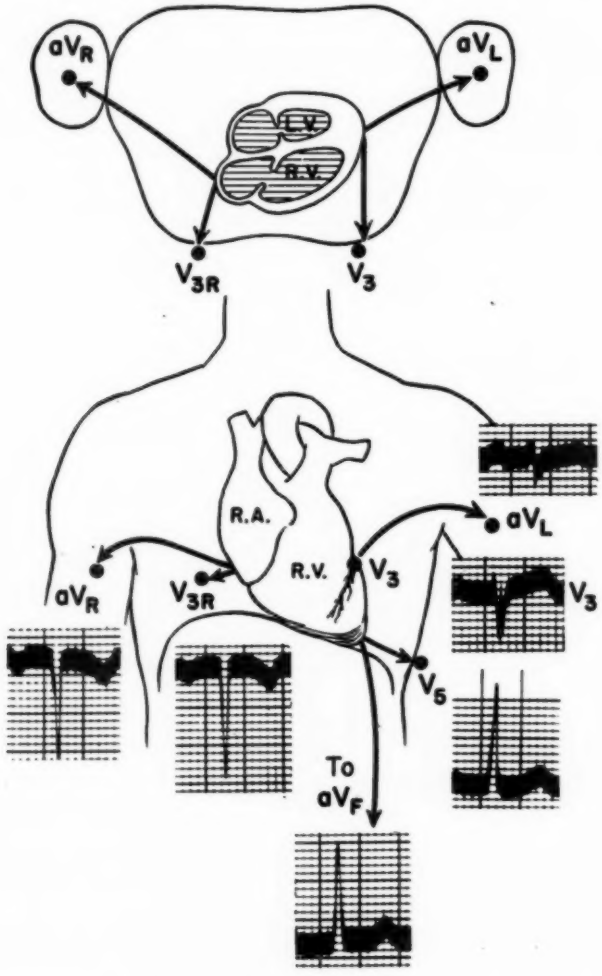

Fig. 6.—Relation of unipolar limb to precordial leads in the third subject, depicting the findings in semivertical position of the heart.

When the pattern in Lead aV_F resembles that of semidirect leads over the left ventricle and Lead aV_L exhibits a diphasic or multiphasic QRS of low voltage, the heart is in semivertical position. The position of the heart in this case is thus midway between the vertical of Fig. 3 and the intermediate of Fig. 1,*b*. In respect to the longitudinal axis, the heart is rotated clockwise in comparison to

that of the first subject illustrated in Fig. 2, but the clockwise rotation is of lesser degree than that displayed by the second subject and depicted in Fig. 4. Furthermore, the heart is not rotated backward on a transverse axis, as in the second case.

In Figs. 7,*a* and *b* and 8,*a* and *b* unipolar limb leads obtained in the recumbent and seated positions on the fourth subject are reproduced along with selected semidirect leads. Lead aV_R exhibits a constant pattern in both postures, characterized by a QS complex and a negative T wave. Because of the close correspondence to the pattern in Lead V_{3R}, it is probable that the potential variations of the right ventricular cavity were transmitted through the tricuspid orifice across the anterior chest wall to the right arm. The findings in Lead aV_F were also constant in the recumbent and seated positions and closely resembled the tracings obtained at the positions of Leads V_5 and V_6 as well as those at E_{55} and E_{50}. These findings would indicate that the left ventricle was in contact with the diaphragm and that the potential variations of its posteroapical aspect were transmitted to the left leg.

Lead aV_L, recorded in the recumbent position, exhibits a negative P wave, a deep Q, a minute terminal R wave, and an inverted T wave. This pattern differs strikingly from that in any precordial lead, but closely resembles that obtained through an esophageal lead near the upper border of the left atrium, as shown in Lead E_{30}. The pathway along which the pattern recorded through semidirect leads near the upper margin of the left atrium was transmitted into the left arm is revealed by multiple exploratory leads from the left side of the back and left axilla. A pattern similar to that seen in Leads E_{30} and aV_L taken in the recumbent position was obtained from points on the upper left back over the spine of the scapula, as illustrated by representative leads from points *B*, *C*, and *D* in the cross-sectional diagram, Fig. 8,*b*. The deep Q appears in Lead aV_L, not only because of transmission of negative potentials across the upper back into the left arm but also because of failure of transmission of positive potentials from the precordium into the left arm. In records of the first subject reproduced in Fig. 1,*a*, the tall R and upright T of Lead V_5 may be traced up the axilla and into the left arm, whereas in this case the tall R and upright T of Lead V_5 (Point F of the cross-sectional diagram) rapidly diminished as the electrode was moved up the axilla to Point *H* and completely disappeared when the apex of the axilla (Point *I*) was reached. The foregoing records indicate that the superior margin of the left atrium faced toward the left upper back, left arm, and apex of the left axilla, as illustrated in the oblique and cross-sectional diagrams depicting the position of the heart in the recumbent posture. The potential variations of the left ventricular cavity were referred through the mitral orifice and left atrium to the upper part of the left back, left axilla, and left arm, accounting for the deep Q wave in all of these leads. The minute terminal R wave was derived from the posterobasal margin of the left ventricle.

The electrical position of this heart is a variant of the vertical position illustrated in Fig. 3. In both subjects, the potential variations of the posteroapical aspect of the left ventricle were referred to the left leg. In the former the potential variations of the right ventricle were transmitted through the anterior chest

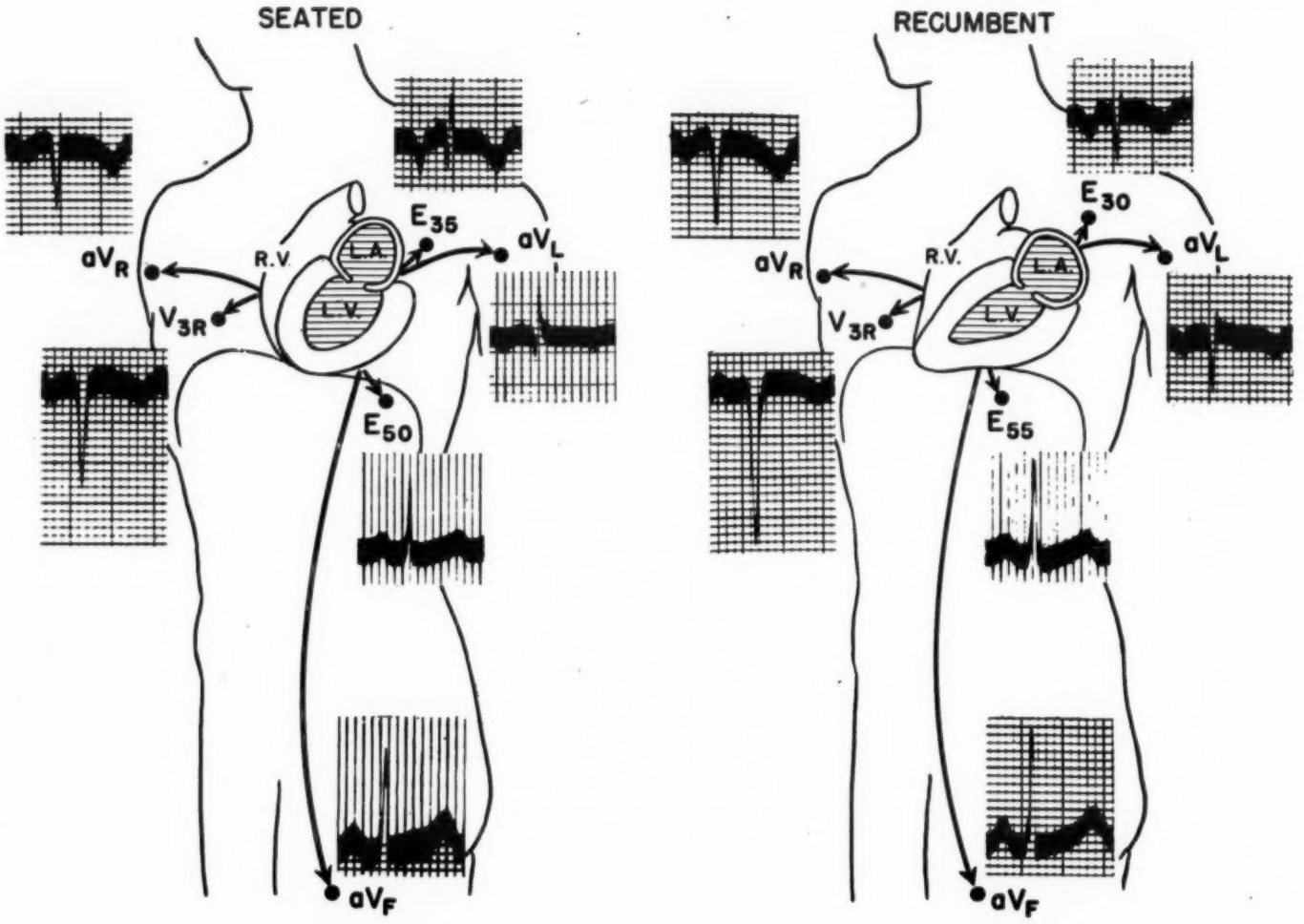

Fig. 7.—Schematic diagram to illustrate postural variations in cardiac position and in the relation of Lead aV_L to esophageal leads in the fourth subject.

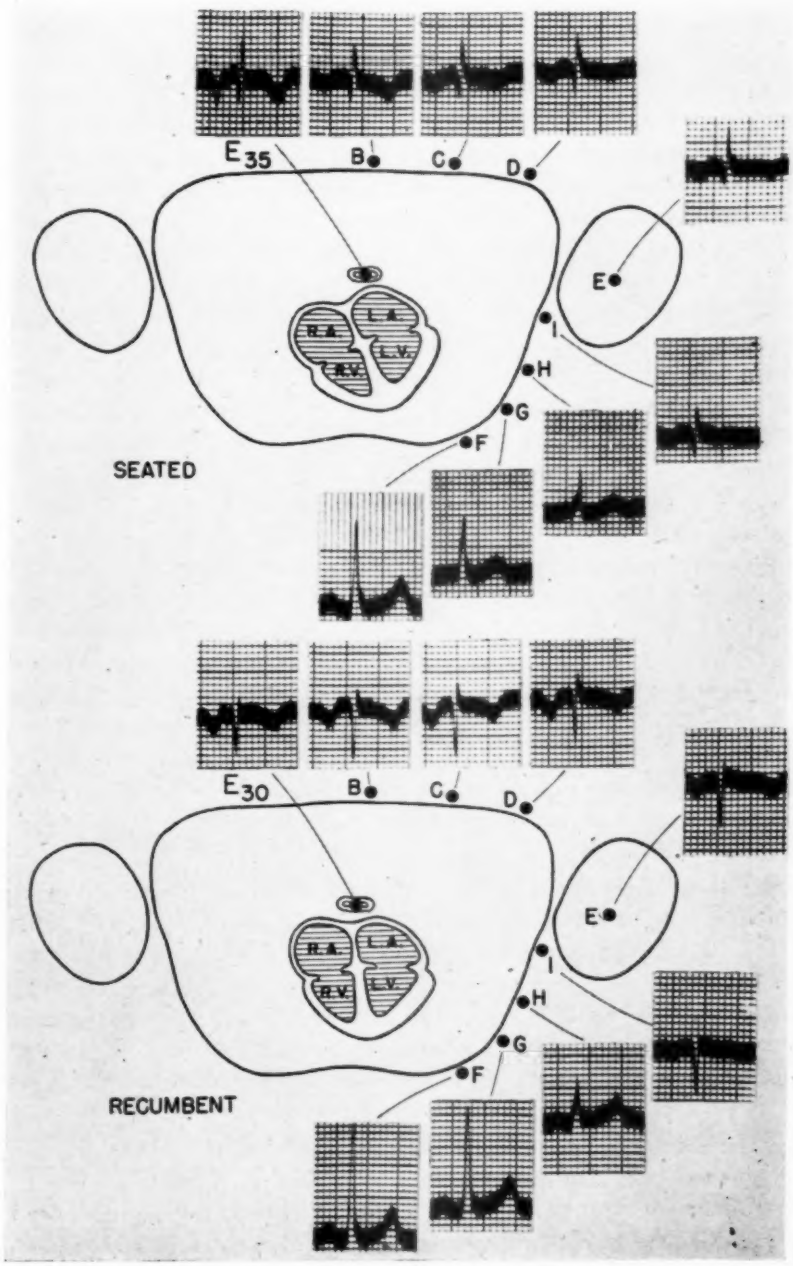

Fig. 8.—Cross-sectional diagrams to illustrate postural variations in cardiac position and the findings in leads from the back and left arm in the fourth subject.

wall to the left arm, whereas in the present subject the potential variations of the upper portion of the left atrium were transmitted through the posterior chest wall to the left arm. These differences may be explicable by differences in degree and direction of rotation about the longitudinal axis. Whereas the pattern in the second subject indicated marked clockwise rotation about the longitudinal axis, as represented in Fig. 4, that in the present subject is indicative of counterclockwise rotation, as represented in Fig. 8,*b*.

In shifting from the recumbent to the seated position, the R wave in Lead aV_L increased considerably at the expense of the Q. Whereas the deep Q and minute R of Lead aV_L, taken in the recumbent position, resembled the pattern of Lead E_{30} high in the esophagus near the upper margin of the left atrium, the relatively small Q and prominent R of Lead aV_L, taken in the seated position, resembled the pattern of Lead E_{35} lower in the esophagus behind the left atrium and nearer the left ventricle. In the seated position, the pattern as registered in Lead E_{35} was transmitted across the left scapula (as indicated by the recordings at Points *B*, *C*, and *D* of Fig. 8,*a*) to the apex of the axilla (as shown by the tracing at Point *I*) and to the left arm. The postural change in pattern is the result of a shift in cardiac position, so that the posterior aspect of the left atrium and the adjoining posterobasal portion of the left ventricle face toward the left arm, as illustrated in the oblique and cross-sectional diagrams of Figs. 7,*a* and 8,*a*. The small Q represents ventricular cavity potentials referred for a brief instant through the mitral orifice, and the relatively large late R was derived from activation of the posterobasal aspect of the left ventricle. The change in Lead aV_L from recumbent to seated position is compatible with a slight backward displacement of the apex in a transverse plane, which would tend to tilt the posterobasal aspect of the left ventricle upward as indicated in Fig. 7, coupled with a slight clockwise rotation on a longitudinal axis, which would favor transmission of the potential variations of the posterobasal aspect of the left ventricle to the left arm.

Since the potential variations of a portion of the epicardial surface of the left ventricle have the dominant effect on both Leads aV_F and aV_L, the electrical position in the sitting posture is a variant of the intermediate position depicted in Fig. 1,*b*. In the present subject the backward displacement of the apex permitted the transmission of the potential variations of the posterobasal aspect of the left ventricle to the left arm, whereas in the first subject the forward displacement of the apex favored the transmission of the potential variations of the anterolateral aspect of the left ventricle to the left arm.

Fig. 9 depicts the precordial leads in the recumbent position and the unipolar extremity leads obtained in the recumbent, sitting, and standing postures on the fifth subject, a young man whose chest was asthenic in type and whose heart was normal to physical and roentgen examination. The pattern in Lead aV_R was not affected by change in posture, and consisted of a QS complex and inverted T wave due to transmission of the potential variations of the atria to the right arm in a manner analagous to that occurring in the first subject. The QRS complex in Lead aV_L showed no significant change of shape with shift in posture. It

consisted of a small R and deep S, which resembled the pattern in Leads V_1 and V_2 and resulted from the transmission of the potential variations of the right ventricle to the left arm in the manner illustrated in the second subject. The change from an inverted to an upright T in Lead aV_L with shift from a recumbent to an erect posture is analagous to the normal fluctuations in the direction of the T wave in Lead V_1. The similarity of the tall R and upright T obtained in Lead aV_F during recumbency to the pattern in Lead V_6 indicates that the potential variations of left ventricle were referred to the left leg and that the heart was in vertical position.

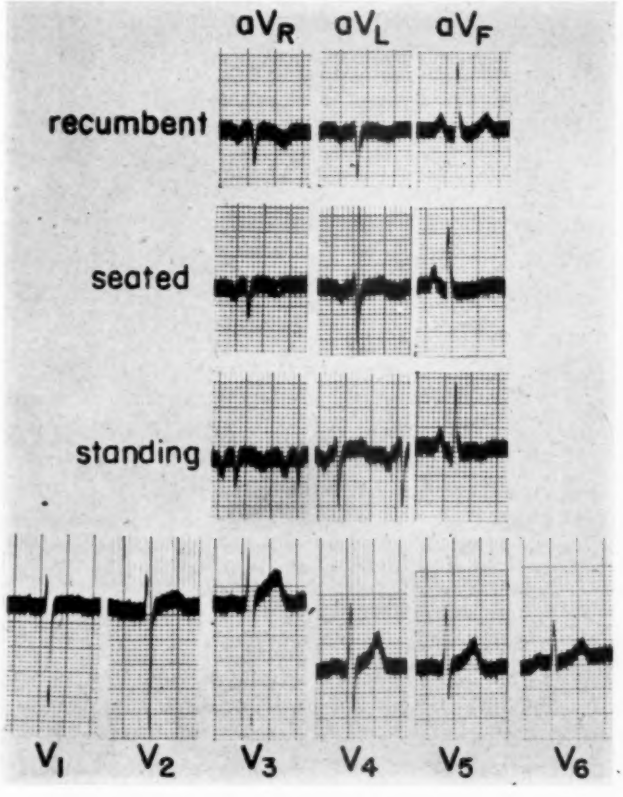

Fig. 9.—Postural variations in Lead aV_F in the vertically placed heart of the fifth subject.

The noteworthy feature of the electrocardiograms of this subject is the change in Lead aV_F with shift in posture from recumbency to sitting to standing. The P wave increased in amplitude and became more sharply peaked in the erect position and a distinct Q wave made its appearance when the subject stood up. The RS-T junction was isoelectric during recumbency and became slightly depressed in the erect position. An upright T wave, 2.5 mm. in amplitude, was recorded in the recumbent position, an isoelectric T wave in the sitting position, and an inverted T wave, 1.0 mm. in depth, in the standing position.

To investigate further the postural variations in the pattern in aV_F, leads were obtained from the lower esophagus in the recumbent and sitting positions. In taking the esophageal leads, the electrode was fixed at its exit from the nose in the attempt to prevent movement of the tip with change of posture. Since the pharynx was well anesthetized and swallowing reflexes were absent, it was believed that the tip remained in a constant position though objective proof through fluoroscopic control was not obtained. With change from the recumbent to seated posture, the P wave in Lead E_{55} increased in amplitude and became more sharply peaked, the RS-T junction became slightly depressed, and the T wave changed from upright to isoelectric. The postural changes in Leads E_{55} and aV_F were identical. The respective tracings are reproduced in Fig. 10

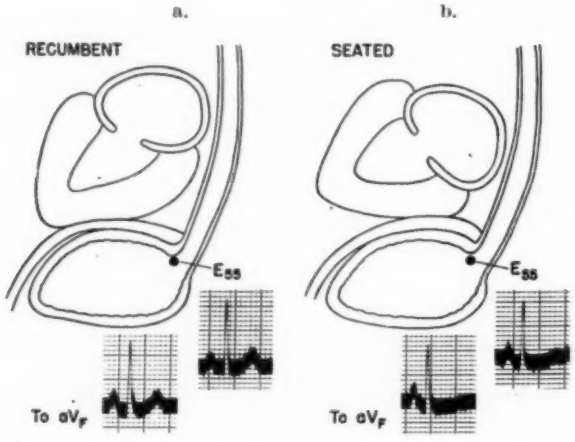

Fig. 10.—Schematic diagram to illustrate postural variations in the relationship of the left ventricle to diaphragm and esophagus in the fifth subject.

along with a diagrammatic representation of the probable changes in the position of heart and diaphragm. With change from the recumbent to erect position, it is probable that the diaphragm descended and flattened, permitting the heart to shift downward and forward. Such a shift would bring the left atrium and atrioventricular groove nearer the lower esophagus and diaphragm and thereby account for the taller, steeper P wave in Leads E_{55} and aV_F. Since semidirect leads from the region of the left atrioventricular groove may normally exhibit a depressed RS-T junction and inverted T, whereas semidirect leads from points near the posteroapical aspect of the left ventricle show an isoelectric RS-T junction and upright T, the depressed RS-T and isoelectric T obtained in the sitting position of this subject may represent an even admixture of potentials from the two areas. These findings are thus in keeping with a closer approach of the posterobasal aspect of the left ventricle to the lower esophagus and diaphragm with change from recumbent to sitting position. The appearance of a Q wave and an inverted T wave in Lead aV_F when the subject stood up lends further support to the hypothesis of a closer approach of the left atrioventricular groove

to the diaphragm. Other factors, such as heightened sympathetic activity,[20] may contribute toward postural variations of the T waves in Lead aV_F, but an exhaustive consideration of the causes of T-wave inversion is beyond the scope of this presentation.

DISCUSSION

Normal Variations in the Augmented Unipolar Limb Leads.—The observations reported in this communication, like those of others,[3,4,6,7,10-15] indicate that the potential variations of a given extremity are dominated by those of the epicardial surface which faces toward that extremity. This is, in turn, dependent upon the anatomic position of the heart. The apical portion of the ventricles which faces toward the left may vary greatly in position, depending upon the shape of the thorax, posture, and phase of respiration, and as a consequence, the pattern in Leads aV_L and aV_F is normally subject to wide variation. On the other hand, the base of the heart which faces toward the right arm is more or less fixed by the attachments to the great vessels, and the pattern in Lead aV_R is more uniform. The normal variations in QRS-T pattern, as correlated with cardiac position, will be classified and summarized separately for each of the three augmented unipolar limb leads.

Lead aV_R: Since the surface of the heart which is directed toward the right arm is made up of the atria and great vessels and includes little or none of the epicardial aspect of either ventricle, the major deflection of ventricular origin in aV_R is derived from the potential variations of the endocardial surfaces and cavities of the two ventricles and consists of a downward QRS and inverted T wave. The basic QRS pattern of aV_R, consisting of a downward major deflection, is subject to four minor variations, namely: (1) a monophasic QS complex; (2) a minute R followed by a deep S; (3) a deep Q followed by a late R; and (4) a small R and R′ separated by a deep S. The mode of origin of each of these variants has been illustrated diagrammatically and discussed at length in a previous communication.[21]

Lead aV_L: The findings in Lead aV_L are normally subject to a much greater variation than those in aV_R because the portion of the heart which extends into the left chest is free to rotate about an anteroposterior, transverse, and longitudinal axis, whereas the basal portion facing toward the right arm is comparatively fixed. While Lead aV_R normally exhibits only one basic QRS-T pattern, subject to four minor variations, the findings pertaining to the ventricular complex of Lead aV_L may be classified into five basic patterns, each with many minor variants. The patterns found in Lead aV_L are appropriately classified in accordance with the semidirect lead which they resemble. If sinus rhythm is present, the P wave in Lead aV_R is always inverted, but that in aV_L may be upright, flattened, diphasic, or inverted, depending upon the position of the heart in the chest.

1. *Pattern in Lead aV_L Resembling That in Semidirect Leads Over the Anterolateral Aspect of the Left Ventricle (V_5 and V_6)*: The anterolateral aspect of the

left ventricle faces toward the left arm when the heart is tilted on its anteroposterior axis into an oblique to horizontal position, and when moderately rotated in a counterclockwise direction on its longitudinal axis. Under these circumstances, the potential variations of the epicardial surface of the anterolateral aspect of the left ventricle are transmitted to Leads V_5 and V_6 and along the pathway leading from these points to the left arm, as illustrated in Fig. 1. The potential variations of the lower part of the left atrium near the atrioventricular groove are transmitted to the left ventricle and thence to the left arm, producing an upright P in aV_L which, like the QRS, resembles that registered in precordial Leads V_5 and V_6. The major portion of the QRS in aV_L consists of an R wave. The time interval from onset to peak of the R wave in aV_L tends to equal or slightly exceed that in Leads V_5 and V_6, but is normally less than 0.04 second. The voltage of R in aV_L is invariably less than the maximum attained in the precordial leads.* Since the decrement in voltage between the epicardial surface and left arm varies with the distance to the left arm and the state of the intervening lung, the amplitude of the R wave may normally range from 1.0 mm. to 15 millimeters. The R wave in aV_L, like that in Leads V_5 and V_6, may be preceded by a small Q wave not exceeding 0.02 second in duration and 25 per cent of the amplitude of the succeeding upright deflection. A small terminal S wave is less common than in Leads V_5 and V_6, but may occur as a normal variant. In place of the Q or S wave, the R may display a notch at the base of its ascending or descending limb within 2.0 mm. of the isoelectric line. Notching or coarse slurring elsewhere on the R wave is abnormal. Notching anywhere on the ascending limb of the R is abnormal if a Q wave is present. The RS-T junction in aV_L is normally isoelectric, but may be slightly elevated if the T wave is tall. The T wave is characteristically upright, but may be within normal limits if flattened.

2. *Pattern in Lead aV_L Resembling That in Semidirect Leads Over the Right Ventricle (Generally V_1 or V_2)*: When the heart drops into a vertical position on its anteroposterior axis and undergoes concomitant clockwise rotation on its longitudinal axis, the anterior wall of the right ventricle may be brought into a position where it faces the left arm, thereby facilitating the transmission of its potential variations across the anterior chest wall into the left arm, as illustrated in Fig. 3. Under these circumstances, Lead aV_L displays a relatively small initial R wave of short duration followed by a relatively deep S wave resembling that registered in precordial leads over the right ventricle (V_1, V_2). Slurring or slight notching of the descending limb of the S wave is occasionally present, analagous to that found in leads just to the right of the transitional zone. The RS-T junction is generally isoelectric, but may be slightly elevated if the T wave is tall. T wave is usually upright, but may be flattened, diphasic, or shallowly inverted, as normally obtains in Lead V_1.

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*In comparing amplitudes of a given deflection in a Goldberger extremity lead with a corresponding deflection in a Wilson precordial lead, it must be borne in mind that technical augmentation of 50 per cent has been obtained in the former and must be corrected for.

3. *QRS-T Pattern in Lead aV_L Resembling That Obtained in Precordial Leads From the Transitional Zone (Generally V_3)*: When the heart is dropped into a more or less vertical position on its anteroposterior axis and rotated moderately in a clockwise direction on its longitudinal axis, the anterior margin of the interventricular septum may face toward the left arm, as illustrated in Fig. 6. Under these circumstances, the general contour of the QRS complex is somewhat like that in a precordial lead at the transitional zone. The QRS complex is low in voltage and consists of two or more phases of approximately equal amplitude. Slurring or notching may be present as a normal phenomenon in these low voltage complexes. The RS-T junction is generally isoelectric and T wave is upright or flattened. When the heart is in vertical to semivertical position, as in Patterns 2 and 3, transmission of potential variations from the upper portion of the left atrium to the left arm is facilitated. The P wave in Lead aV_L tends to be diphasic to inverted and is thus comparable in direction to the P wave registered through esophageal leads from behind or above the atrium. Hence, the contour of the P wave in Lead aV_L provides supplemental evidence as to the position of the heart in the chest and its rotation on an anteroposterior and longitudinal axis.

4. *QRS-T Pattern in Lead aV_L Resembling That in Esophageal Leads Opposite the Posterior Aspect of the Left Ventricle*: Rotation of the heart on its transverse axis to bring the apex backward may cause sufficient tilting so that the posterior wall of the left ventricle faces toward the left arm, as illustrated in Figs. 7,*a* and 8,*a*. Under these circumstances, a pattern is obtained in aV_L which resembles that from esophageal leads at the ventricular level. The main component of the QRS is upright and the time interval from its onset to peak is less than 0.04 second. The R wave is characteristically preceded by a Q, which is ordinarily less than 0.03 second in duration and generally less than 25 per cent of the amplitude of the succeeding upright deflection. Slurring or notching near the base of the upstroke of the R may take the place of the Q wave. The relationships of Q to R will depend upon the portion of the posterior surface having the predominant effect upon the record in aV_L, the Q wave increasing at the expense of the R when portions near the atrioventricular groove are largely represented. The T wave is ordinarily upright, but may be inverted if the dominant effect is coming from the region about the atrioventricular groove. Under such circumstances the P wave may show a steep downward deflection reaching below the isoelectric line, which is a remnant of the intrinsicoid deflection recorded through esophageal leads near the auriculoventricular junction.

5. *QRS-T Pattern in Lead aV_L Resembling That in Esophageal Leads From Behind or Above the Left Atrium*: When the heart is dropped into vertical position and displays counterclockwise rather than the usually associated clockwise rotation on its longitudinal axis, the potential variations from the left atrium and mitral orifice may be referred to the left arm, resulting in a deep and prolonged Q, usually followed by a small R derived from the posterobasal aspect of the left ventricle, as illustrated in Figs. 7,*b* and 8,*b*. The relationship of Q to

R will depend upon the region having the predominant effect upon the tracing. The Q is large and the R is small or absent when the upper part of the atrium is represented; the R increases at the expense of Q when the area of reference is closer to the atrioventricular junction. An inverted P wave resembling that in esophageal leads from above the heart and an inverted T wave are characteristic features of this pattern. The prominent Q, small R, and inverted T, occurring in Lead aV_L when the heart is so placed that the potential variations of the left atrium are referred to the left arm, resembles the pattern found in aV_L when an infarct of the lateral wall of the left ventricle faces toward the left arm. When the potentials of the left atrium are responsible, the associated P wave is characteristically inverted; when there is involvement of the lateral wall of the left ventricle, the P wave is usually upright. A normal Q-R pattern in Lead aV_L can usually be modified greatly by posture, the R tending to increase at the expense of Q with shift from recumbent to erect posture (Fig. 7).

Lead aV_F: If sinus rhythm is present. the P wave in Lead aV_F should be upright. The QRS-T pattern in aV_F, like that in aV_L, is subject to considerable variation among normal persons, owing to the capacity of the apical portion to rotate about an anteroposterior, transverse, and longitudinal axis. A given rotation tends to produce effects in aV_F that are reciprocal to those in aV_L. The ventricular complex in Lead aV_F may be classified into four basic patterns, each with numerous minor variations.

1. *QRS-T Pattern in Lead aV_F Resembling That in Precordial Leads Over the Right Ventricle (V_1 and V_2)*: The QRS consists of a small initial R of brief duration followed by a relatively deep S, resembling that of Leads V_1 or V_2, as illustrated in Fig. 1,*a*. Rarely a QS complex may be obtained in aV_F, analagous to that occurring as a normal variant in Lead V_1. The rare normal QS complex of aV_F may be mistaken for posterior infarction, but is differentiated by its inconstancy with respiration and changes of posture. An initial R tends to appear phasically with respiration and is usually demonstrable when the electrocardiogram is repeated in another posture. The RS-T junction is characteristically isoelectric, but may be elevated if the T wave is tall and upright. The T wave is generally upright, but may be flattened, diphasic, or inverted, as normally obtains in Lead V_1. When the foregoing pattern is present in aV_F, a small R and deep S will generally be found in leads from the lower esophagus and stomach. This pattern in aV_F is associated with a prominent R in aV_L and is a result of concomitant counterclockwise rotation about an anteroposterior and longitudinal axis into a horizontal position.

2. *QRS-T Pattern in Lead aV_F Characterized by a Diphasic or Multiphasic Complex of Low Voltage*: This pattern may be obtained when the potential variations of the diaphragm and points below are dominated by those of the interventricular septum, as illustrated in Fig. 5. The upward and downward deflections of the QRS are approximately equal in amplitude and may appear slurred or notched. The RS-T junction is isoelectric and the T wave is generally upright, but may be flattened. A comparable pattern may usually be recorded

from the lower esophagus or stomach. Such a finding in Lead aV_F, accompanied by a prominent R wave in aV_L resembling that in Leads V_5 and V_6, occurs with a lesser degree of counterclockwise rotation into a semihorizontal position.

3. *QRS-T Pattern in Lead aV_F Resembling That in Semidirect Leads From the Apical Portion of the Left Ventricle (Precordial Leads V_5 and V_6 and Leads From the Lower Esophagus or Stomach)*: This pattern is found when the heart is in an oblique to vertical position in reference to its anteroposterior axis and rotated sufficiently in a clockwise direction on its longitudinal axis so that potential variations of the posterior apical wall of the left ventricle are transmitted to the diaphragm and thence to the left leg, as illustrated in Figs. 1,*b*, 3, and 6. Under such circumstances, the main deflection of the QRS is an R wave. The time interval from onset to peak of the R tends to equal or slightly exceed that in Leads V_5 and V_6. The voltage of the R in aV_F ranges from 1 to 20 mm. and is usually less, but occasionally greater, than that in the precordial leads. The R wave, like that in V_5 and V_6, is often preceded by a small Q not exceeding 0.02 second in duration and 25 per cent of the amplitude of the succeeding upright deflection. A small S wave may be present. Notching or slurring may occur under circumstances similar to those described in connection with the pattern of Lead aV_L. The RS-T junction is characteristically isoelectric and the T wave upright, but may be flattened as a normal variant. Such a QRS-T complex in Lead aV_F may be associated with a corresponding pattern in aV_L (that is, Pattern 1) if the heart is in intermediate position and rotated forward on a transverse plane; or with a negative P, QR, and flattened to inverted T in aV_L if the heart is in intermediate position and rotated backward on a transverse plane; or with a low voltage diphasic complex in aV_L if in semivertical position; or with a small R and deep S in aV_L if in vertical position and rotated clockwise on its longitudinal axis; or with a prominent Q and late R in aV_L if in vertical position and rotated counterclockwise on its longitudinal axis.

4. *Pattern in Lead aV_F Resembling That in Esophageal Leads Opposite the Posterobasal Aspect of the Left Ventricle*: This may occur rarely as a normal variant when the heart is in vertical position with apex displaced forward so as to bring the posterobasal aspect into closer apposition to the diaphragm, thereby facilitating the transmission of its potential variations to the lower part of the body, as illustrated in Fig. 10,*b*. The pattern in Lead aV_F resembles that obtained in esophageal leads near the atrioventricular groove. The QRS is characterized by a distinct Q wave, 0.03 second or less in duration and fairly large in amplitude, and a relatively tall R, which generally is more than four times the amplitude of the Q. The RS-T junction may be isoelectric or slightly depressed. The T wave is typically inverted, diphasic, or flattened, but may be upright. This normal variant may be mistaken for posterior infarction and may require esophageal leads for differentiation. The normal QR is modified more by respiration and posture, the Q wave generally decreasing on recumbency.

Relation of the Unipolar Limb Leads to the Standard Extremity Leads.— Whereas the Wilson and Goldberger limb leads are essentially unipolar, the

standard limb leads are bipolar in that the two extremities which are connected through the galvanometer will have an approximately equal, though opposite, effect upon the resultant tracing. Wilson and associates[22] demonstrated that the tracings obtained through Leads I, II, and III could be calculated mathematically from known unipolar extremity potentials from the right arm, left arm, and left leg (V_R, V_L, and V_F). By transposing these values into Einthoven's equation, they showed that Lead I must equal $V_L - V_R$; Lead II = $V_F - V_R$; and Lead III = $V_F - V_L$.

The recordings through the Goldberger leads may be used in the preceding equations if the result is multiplied by two-thirds. Hence, Lead I equals aV_L minus aV_R times two-thirds. For the average person, subtraction is more difficult than addition, particularly when dealing with both a positive and a negative value. When confronted with a problem of subtracting a negative from a positive value, the same answer may be derived more easily by adding the reciprocal of the negative to the positive. In other words, an identical answer will be obtained by modifying this formula as follows: Leads I equals aV_L plus the reciprocal of aV_R times two-thirds. In applying this formula to the derivation of Lead I, it will be necessary to mentally invert the pattern recorded in Lead aV_R.

The application of the original and the modified formula for the derivation of each of the standard leads from the constituent unipolar limb leads is illustrated in Fig. 11. The records reproduced in Part *A* are from the first subject, whereas those in Part *B* are from the second subject. The use of the two variations of the formula is illustrated by the derivation of the initial deflection of standard Lead II of Case *A*:

$$\textit{Lead II} = aV_F - aV_R \times 2/3$$
$$+0.9\ mv. = +0.4\ mv. - (-1.2\ mv.)\ or\ +1.6\ mv. \times 2/3 = (1.1\ mv.)$$

or

$$\textit{Lead II} = aV_F + \textit{reciprocal of}\ aV_R \times 2/3$$
$$+0.9\ mv. = +0.4\ mv. + 1.2\ mv.\ or\ +1.6\ mv. \times 2/3 = (1.1\ mv.)$$

The values calculated from the unipolar leads approximate, but are not identical with, the values actually recorded in the standard leads. Differences may be observed even though standardization is perfect, and arise when potentials of the two extremities are varying in the same direction. During the registration of the latter part of the QRS in Leads aV_F and aV_R in the first subject, the potentials of the right arm and left leg were varying in the same direction, as shown by the fact that a downward deflection was being recorded in each lead; however, the galvanometric connections to the right arm in Lead II are the opposite of those to the left leg, and the potential variations which produce a downstroke with right arm connections, as in Lead aV_R, will produce an upstroke with connections as in Lead II. Thus, the simultaneous upstroke from the right arm connections and the downstroke from the left leg connections will partially neutralize one another and the resultant R wave in Lead II will be

smaller than that calculated from Lead aV_R and the S wave in Lead II will be smaller than that calculated from Lead aV_F.

The main contribution of the unipolar limb leads to the analysis of the standard leads lies in the information provided as to the source of the deflections in the standard leads. The RS pattern in Lead II of the first subject is almost identical in contour with that in the second subject, but was of quite

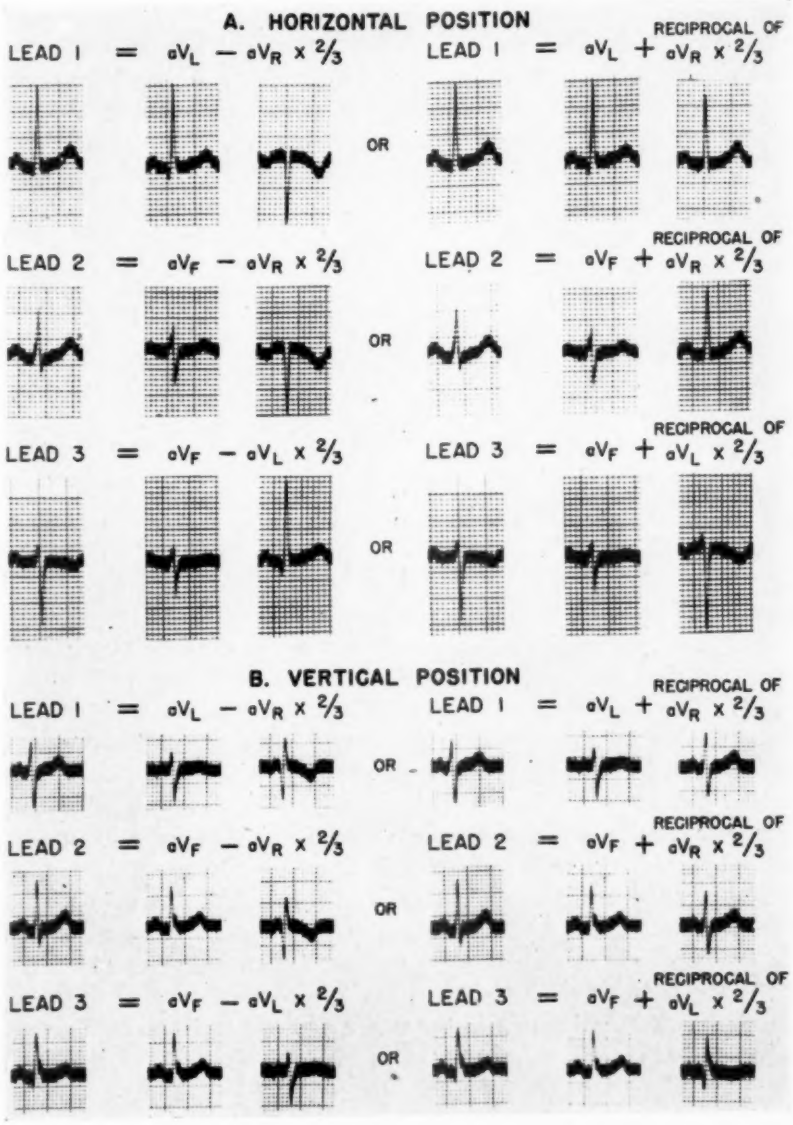
A. HORIZONTAL POSITION
LEAD I = aVL − aVR x 2/3
OR
LEAD I = aVL + RECIPROCAL OF aVR x 2/3
LEAD 2 = aVF − aVR x 2/3
OR
LEAD 2 = aVF + RECIPROCAL OF aVR x 2/3
LEAD 3 = aVF − aVL x 2/3
OR
LEAD 3 = aVF + RECIPROCAL OF aVL x 2/3
B. VERTICAL POSITION
LEAD I = aVL − aVR x 2/3
OR
LEAD I = aVL + RECIPROCAL OF aVR x 2/3
LEAD 2 = aVF − aVR x 2/3
OR
LEAD 2 = aVF + RECIPROCAL OF aVR x 2/3
LEAD 3 = aVF − aVL x 2/3
OR
LEAD 3 = aVF + RECIPROCAL OF aVL x 2/3

Fig. 11.—Derivation of the standard limb leads from the augmented unipolar limb leads. *a*, In horizontal cardiac position, as illustrated by records from the first subject. *b*, In vertical cardiac position, as illustrated by records from the second subject.

different origin, as is evident from a study of the unipolar leads. R_2 of the former was derived chiefly from the potential variations of the right arm, and the S wave was derived exclusively from the potential variations of the left leg, as shown by its presence in aV_F and its absence in the reciprocal of aV_R. On the other hand, R_2 of the second subject came chiefly from the potential variations of the left leg, and S_2 came exclusively from the potential variations of the right arm, as shown by its presence in the reciprocal of aV_R and its absence in aV_F. T_3 of both subjects represents a blend of an upright component from the left leg and a downward component from the left arm. The resultant T_3 is inverted in the first subject because of the greater amplitude of the negative component from the left arm, and is upright in the second subject because of the greater amplitude of the upright component from the left leg. More important is the information provided as to the origin and significance of Q waves. Q_1 of the first subject is carried over from the normal Q of aV_L. Q_3 of the second subject also came from the potential variations of the left arm, but the derivation was quite different. The left arm potentials during ventricular activation in this subject were initially positive and subsequently negative. This registers as an RS complex when the left arm is connected to the positive pole of the galvanometer,* as in Lead aV_L, and as a QR complex when the left arm is connected to the negative pole, as in standard Lead III. When the Q wave in a standard lead is large, its origin and significance may be obscure unless unipolar extremity leads are available.

In comparing the standard leads of the two subjects, it should be recalled that their respective precordial Leads V_1 and V_2 were much alike and, furthermore, that Leads V_6 and V_7 of the second subject resembled V_5 and V_6 of the first. The standard leads, however, show a striking difference. The main deflection of Lead I of the first subject is upright, whereas that of Lead III is downward. The prominent R_1 is due chiefly to the fact that the potential variations of the left ventricle were referred to the left arm and were thus carried over into Lead I. The deep S wave in Lead III is also due chiefly to reference of the potential variations of the left ventricle to the left arm. Since the left arm is connected to the positive pole of the galvanometer in Lead I and to the negative pole in Lead III, the electromotive forces which give rise to an upward deflection in Lead I will produce a downward deflection in Lead III. In the tracings of the second subject the main deflection in Lead I is downward and in Lead III, upward. The prominent S wave in Lead I of this case is due partially to transmission of potential variations of the right ventricle to the left arm and partially to transmission of potential variations from the posterobasal surface of the left ventricle to the right arm. Thus, the deep S wave carried over from Lead aV_L is reinforced by that derived from the reciprocal of Lead aV_R. The prominent R wave in Lead III is due chiefly to the fact that potential variations of the left ventricle were referred to the left leg. The slurring on the descending limb of R_3 is carried over directly from Lead aV_F. These examples merely illustrate

*The term, *positive pole of the galvanometer*, is used as a convenience for descriptive purposes and refers to that connection of the exploring electrode which will yield an upright deflection if the potential of the exploring electrode is relatively positive.

the wide variations in electrical axis that may occur in the electrocardiograms of normal persons as a result of differences in the position of the heart within the chest.

If unipolar limb leads and multiple precordial leads are available, standard limb leads are superfluous. They contribute no information that cannot be derived more precisely from the unipolar limb leads studied in conjunction with multiple precordial leads. The main reason for continuance in this laboratory is for comparative purposes in return cases in which the standard leads were the only available limb leads.

SUMMARY

Multiple semidirect leads from the thorax and esophagus along with the augmented unipolar limb leads were obtained in normal subjects in the recumbent and erect postures during quiet breathing and sometimes during forced expiration and full inspiration as well. If a sufficient number of semidirect leads were taken, the counterpart of the QRS-T pattern of each of the unipolar limb leads could be demonstrated in a precordial or esophageal lead and a pathway along which the QRS-T complex maintained a fairly uniform configuration could be found bridging the gap between the extremity and the point on the thorax near the heart where the corresponding semidirect lead was obtained. From the anatomic position of the corresponding semidirect lead and of the pathway leading into the extremity, it was concluded that the potential variations of a given extremity are dominated by those of the epicardial surface which faces toward that extremity.

The findings are presented graphically for five subjects, who were selected as collectively illustrative of the normal variations in QRS-T pattern in unipolar limb leads. The illustrations include the marked variations which may be produced by postural or respiratory shifts in cardiac position. The QRS-T pattern in each of the unipolar limb leads was classified in accordance with the corresponding semidirect lead.

The findings in Lead aV_L were classified into the five basic patterns: (1) QRS-T resembling that in semidirect leads over the anterolateral aspect of the left ventricle (Leads V_5 and V_6) and characterized by a prominent R with or without a small Q and/or S, preceded by an upright P and followed by an upright T; (2) QRS-T resembling that in semidirect leads over the anterior aspect of the right ventricle (Leads V_1 and V_2) and characterized by a small R, relatively deep S, and by a T wave which is usually upright, but occasionally flattened or shallowly inverted; (3) QRS-T resembling that in precordial leads at the transitional zone (generally Lead V_3) and characterized by a QRS of low voltage, consisting of two or more phases of approximately equal amplitude; (4) QRS-T resembling that in esophageal leads opposite the posterior aspect of the left ventricle and characterized by a relatively small Q and tall R preceded by an inverted P wave and followed by an upright, flattened, or inverted T; and (5) QRS-T resembling that in esophageal leads from behind or above the

left atrium and characterized by a relatively deep and prolonged Q and small late R, preceded by an inverted P and followed by an inverted T.

The findings in Lead aV_F usually corresponded fairly closely with those in leads from the lower esophagus and stomach and were classifiable into four basic patterns: (a) QRS-T resembling that in precordial leads over the right ventricle (Leads V_1 and V_2) which was associated with Pattern 1 in aV_L as a manifestation of counterclockwise rotation into a horizontal position; (b) QRS-T resembling that in leads at the transitional zone, which was also associated with Pattern 1 in aV_L as a manifestation of less counterclockwise rotation into a semihorizontal position; (c) QRS-T resembling that in leads from the apical portion of the left ventricle (Leads V_5 and V_6 and lower esophageal leads) which might be found in association with any of the five patterns in Lead aV_L, depending upon the degree of rotation on the anteroposterior, longitudinal, and transverse axes into an intermediate, semivertical, or vertical position; and (d) QRS-T resembling that in esophageal leads opposite the posterobasal aspect of the left ventricle, characterized by a distinct Q, tall R, isoelectric to slightly depressed RS-T, inverted, diphasic, or flattened T, and accompanied by Patterns 2 or 5 in Lead aV_L, depending mainly upon the rotation on the longitudinal axis.

While the pattern in Leads aV_L and aV_F is subject to marked variation due to the mobility of the ventricles in the left chest, the pattern in Lead aV_R is more uniform due to the fixation of the base of the heart, which faces toward the right arm, by the attachments to the great vessels. The major deflection of ventricular origin in Lead aV_R is derived from the potential variations of the endocardial surfaces and cavities of the two ventricles and consists of a downward QRS and inverted T wave. Minor variations may occur in Lead aV_R, consisting of either or both of the following: (1) a minute initial R transmitted from the epicardial surface of the right ventricle across the anterior chest wall; or (2) a late R which tends to be transmitted from the posterobasal surface of the left ventricle across the posterior chest wall when the heart is rotated backward on a transverse axis.

The standard limb leads have been analyzed in terms of unipolar limb leads. If unipolar limb leads and multiple precordial leads are available, standard leads are superfluous, since they contribute no information that cannot be derived more precisely from the unipolar limb leads, studied in conjunction with multiple precordial leads.

The illustrations were made by Miss Evelyn Erickson, assisted by Miss Geraldine Chesney.

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A NEW ELECTRONIC METHOD FOR SIMULTANEOUS RECORDING OF THE BALLISTOCARDIOGRAPH AND ELECTROCARDIOGRAPH

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FOR the benefit of others who may build a ballistocardiograph, we describe here a convenient electronic device, with simultaneous electrocardiogram, for the recording of table oscillations induced by the heart beat, the need for which became apparent while working with a light-mirror method of recording. By the latter method, the assemblage and adjustments necessary to obtain a record so reduced its practicability that few combined tracings resulted. To eliminate these disadvantages we devised a compact, simply operated method incorporating at least four improvements: (1) a control unit which may be located any desired distance from the table; (2) no intricate adjustments required before operation; (3) the record thus obtained depicts the electrical stimulus initiating the ballistocardiographic movements; and (4) the recording unit can be adapted to most forms of ballistocardiographic tables.

DESCRIPTION OF APPARATUS

The completed system of recording will be divided into a number of individual units to facilitate description. The units are diagrammed and each is discussed separately (see Fig. 1).

A. *High-Frequency Oscillator*.—The oscillator is the first unit used in the conversion of the physical movements of the table into voltage change. This is accomplished by altering the oscillator frequency through variance in capacitance. Two small circular brass plates are used. One plate is mounted on the moving table; the other to its frame, so that a variation in distance between these two plates by motion of the table results in a corresponding change in oscillator frequency. Our oscillator has a frequency of approximately 54 megacycles. A high frequency is used with frequency modulation because the width of a given frequency band in the high-frequency range is much wider than that obtained in the standard broadcast range.

To facilitate ease of adjustment of the distance between the plates, an adjustable micrometer has been added (Fig. 2).

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B. *Receiver.*—The frequency of the oscillator is transmitted to a commercial Frequency Modulation receiver through a coaxial cable. The audio section, speaker, and automatic volume control circuit were removed from this receiver and a tuning eye (6U5) was added to aid in the selection of the resonance tuning point.

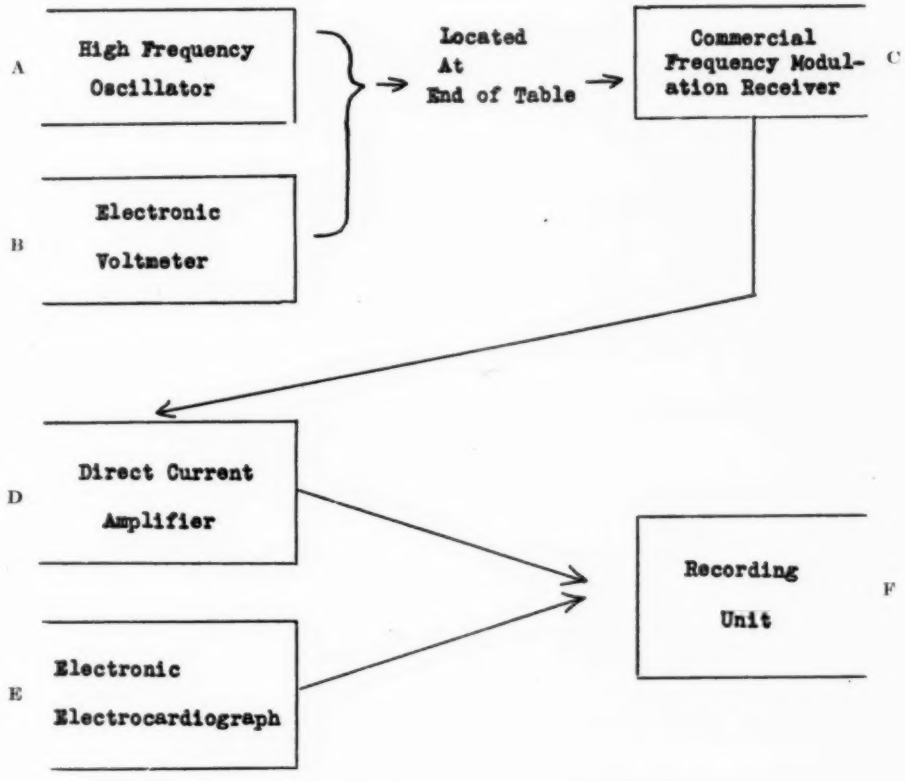

Fig. 1.—Schematic diagram of complete system.

C. *Electronic Voltmeter.*—A zero center, electronic voltmeter is used for the final careful adjustment of the resonance point of the receiver. For convenience, it is located alongside the oscillator on the frame of the table (see Fig. 2).

D. *Direct Current Amplifier.*—In order to adjust the output voltage from the receiver to our recording mirror galvanometers, it became necessary to increase the voltage output of the receiver. This was done by connecting the output of the receiver (cathode of the 6H6) directly into a low-gain direct current amplifier. The amplifier contains three push-pull stages, with the final stage used as an impedance coupling from the tube to the mirror galvanometer (Fig. 3).

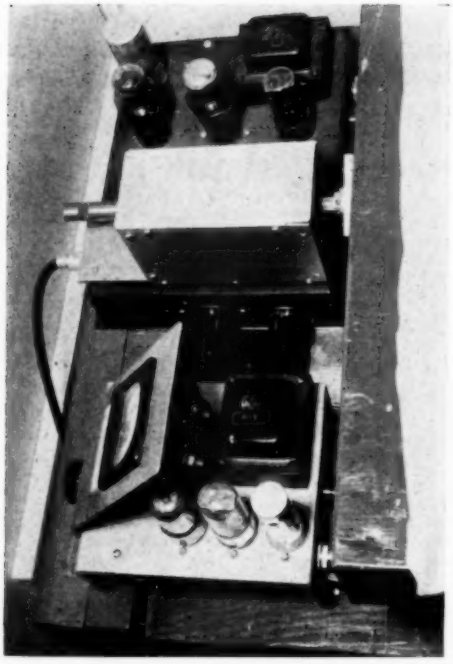

Fig. 2.—Oscillator and voltmeter.

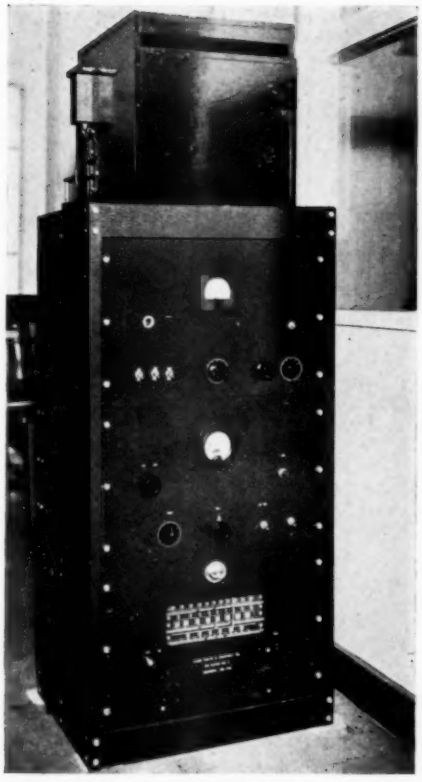

Fig. 3.—Complete apparatus.

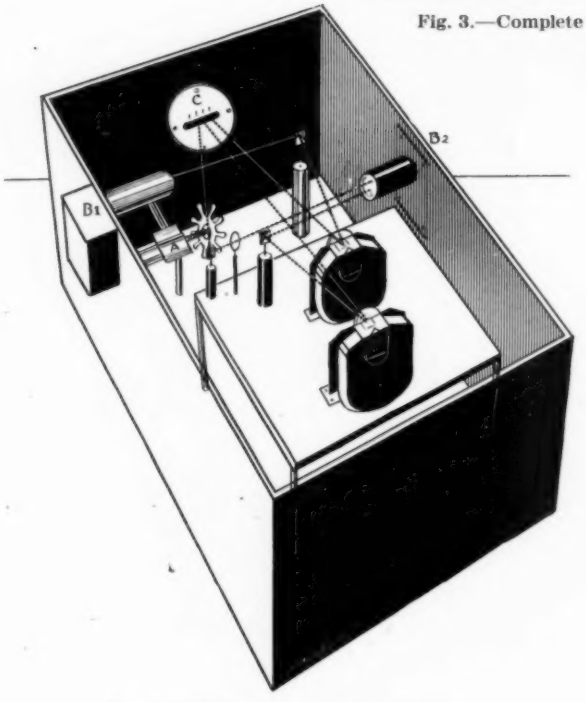

Fig. 4.—Diagram of recording system.

E. *Electronic Electrocardiograph.*—To complete this unit, an electrocardiograph was constructed. This amplifier contains four resistance coupled stages with characteristics similar to those available commercially.

F. *The Recording Unit.*—The assembly of the recording unit is diagrammed in the accompanying photograph. Two Sanborn mirror galvanometers are focused into a Sanborn camera with the beams reflected by means of prisms. The timer consists of a 300 r.p.m. synchronous motor with a revolving disc allowing the light beam to be recorded every four-hundreths of a second (see Fig. 4).

Operation.—In order to operate this assembly, one merely allows a period of "warming-up" of all units. Careful adjustment is made of the exact resonance point as indicated by the electronic voltmeter, with the patient resting on the table. The mirror galvanometers are then adjusted to their relative positions on the camera aperture. The camera is then turned on and the photographic paper provides a permanent record. For continuous observance of the ballistocardiograph pattern, a cathode ray oscillograph was connected to the output of the receiver.

RESULTS

The table used is one obtained from the Department of Physiology and is of the high-frequency type, compared with that described by Starr and associates.[1] Its characteristics are listed in Table I.

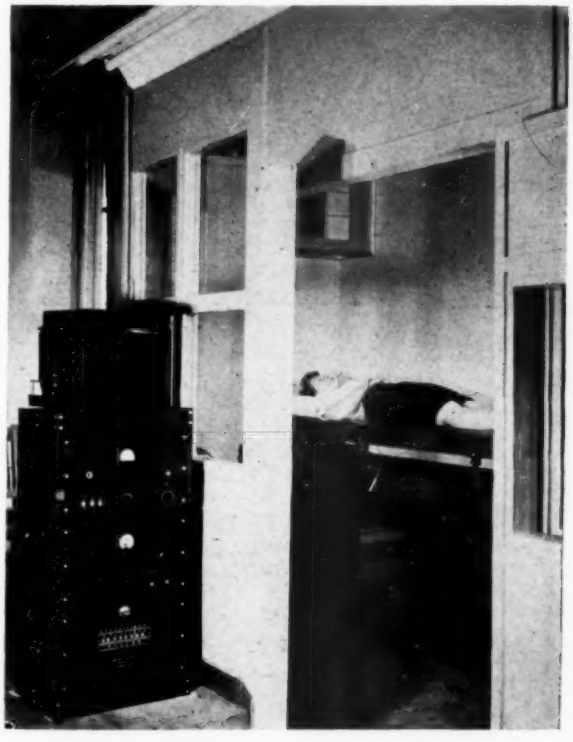

Fig. 5.—View of apparatus and position in relation to table.

Since the controlling apparatus for the recording device is remotely placed from the table one can easily obtain multiple records and under changing environmental conditions in a special chamber (Fig 5). It was actually this need that stimulated the construction of this new apparatus. With such a recording system one is able to carry out frequent acute experiments, and the simultaneously recorded electrocardiogram is an invaluable aid in studying and comparing the electrical cardiac impulses along with their respective mechanical components.

Fig. 6 shows reproductions of Leads I, II, and III of the electrocardiogram and simultaneous ballistocardiogram. Note the ventricular premature contraction in Tracing *B*.

Fig. 6.—Normal ballistocardiograms.

Several abnormal ballistocardiographic tracings are presented in Fig. 7. The dual system of recording facilitates the study of both electrical and mechanical events occurring in the cardiac cycle.

Fig 7,*A* is a tracing on a 28-year-old man with severe aortic insufficiency. The systolic blood pressure was 300 mm. Hg; the diastolic could not be determined since the sounds were heard to 0. Note the enormous stroke volume pattern of the ballistocardiogram. Although this represents the actual stroke

volume, a considerable volume is returned to the ventricle by regurgitation through the valve.

The tracing of Fig. 7,*B* is that of a 54-year-old man with angina pectoris of one year's duration. The physical examination was negative and the electro-

TABLE I. CHARACTERISTICS OF OUR TABLE COMPARED WITH THOSE OF STARR'S

FREQUENCY OF TABLE		STARR'S TABLE	
No wgt. added	40.8		
50 lbs. dead wgt.	15.7	50 lbs.	15.5
100 " " "	13.4	100 "	12.5
150 " " "	11.5	150 "	10.5
200 " " "	10.7	200 "	9.5
268 " " "	9.0		

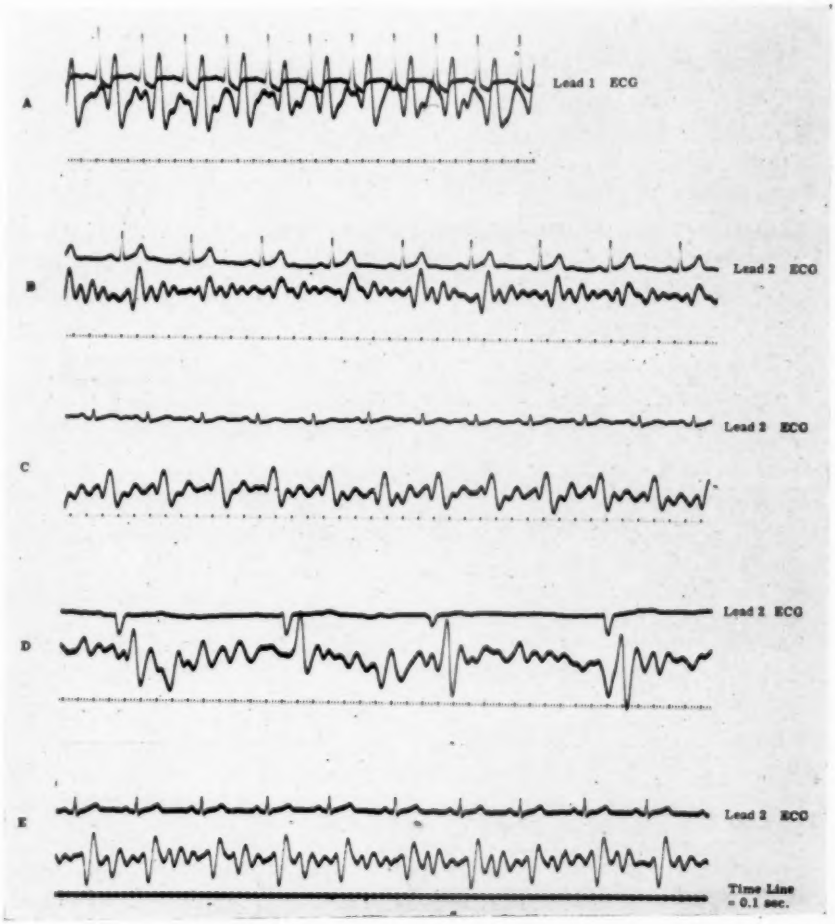

Fig. 7.—Abnormal ballistocardiograms.

cardiogram is normal. The ballistocardiographic pattern reveals variations in successive cycles which may be attributed to respiration.[2] Note the changes occurring in the ballistocardiographic pattern as the amplitude diminishes.

The tracing of Fig. 7,*C* is that of a 38-year-old woman with a blood pressure of 160/90 and moderate angina pectoris of eight months' duration. Note the diminished depth of the I wave and increased depth of the K wave.

Fig. 7,*D* shows the tracing obtained on a 73-year-old man with complete heart block. Note the tendency of the complexes to approach the normal despite the severe heart disease.

Fig. 7,*E* shows the tracing obtained on an 11-year-old boy with coarctation of the aorta. Note the deep I wave and shallow K wave as contrasted with the normal tracing in Fig. 6,*A*. This is a consistent finding in a series of four cases of coarctation.

SUMMARY

1. An electronic dual recording apparatus is described and illustrated. Simultaneous tracings of the electrocardiogram and ballistocardiogram can be obtained with this apparatus.

2. Both normal and abnormal tracings are reviewed in order to demonstrate some of the results obtained.

The authors wish to express their appreciation to Dr. William S. McCann for his valuable suggestion and criticism, and to Dr. H. A. Blair for technical advice and assistance in construction of the apparatus.

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SEASONAL VARIATIONS IN HEART AND CORONARY DISEASE AS RELATED TO VARIOUS ENVIRONMENTAL FACTORS

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MANY investigators have searched for a possible relationship between environmental temperature and heart disease. Some physicians have the impression that a lowered environmental temperature has a deleterious effect on patients suffering from heart disease and, more specifically, coronary heart disease. If this harmful effect exists, one should be able to demonstrate that definite seasonal changes occur in these groups.

In order to minimize the inaccuracies of diagnoses entered on death certificates, it was necessary to analyze a large number of deaths. The largest available series in one specific area with similar environmental conditions is that found in the City of New York. This study is therefore, restricted to the vital statistics[1] and meteorological data[2] available in this area.

Certain other factors are known to influence mortality statistics, and their effects should be minimized as far as possible. These factors and their mode of elimination will be outlined.

Number of Cases.—In order to obtain a large series of cases, the data were analyzed for a ten-year period from 1934 to 1944. It was found that a total of 520,041 people had allegedly died from causes other than heart disease. A total of 470,836 people died from all types of heart disease. No data are available for deaths resulting from coronary heart disease until 1940. Therefore, the data for deaths due to coronary disease were analyzed for a five-year period only, namely from 1940 through 1944. A total of 35,202 coronary deaths occurred in this period. For emphasis it should be noted that this study comprises a total of over one million deaths.

Seasonal Variation.—All deaths, other than deaths from heart disease, in New York City exhibit a definite variation with seasons. They are appreciably lower in the summer months than in the winter months. To demonstrate a seasonal variation in all forms of heart disease, and specifically, in those due to coronary heart disease, it is necessary to compare these deaths with the seasonal variation that occurs in deaths due to all other causes. This was done by removing mathe-

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matically the seasonal variation of all causes of death other than those due to heart disease. Practically, this amounts to holding one variable constant (namely, deaths due to all other causes) and calculating the changes that will appear in the other variable (namely, those deaths due to heart disease as a whole, and coronary heart disease as one type).*

Population Changes.—Since population varies markedly, it is necessary to minimize the effect of this change. In this study the population has been held fairly constant for the ten-year period by expressing each monthly death rate in per cent of the total deaths for each year. Thus, the effect of the gradual increase in population is eliminated.

RESULTS

The question remains whether a significant seasonal variation exists in deaths due to heart disease as a whole, and coronary disease as a group, when the previously discussed factors were minimized. Fig. 1 may be interpreted as showing a positive result. The deaths for all other causes are represented as a straight line and the changes of heart disease and coronary disease are plotted as they vary about this baseline. It is to be noted that a difference of 18.8% appears between the maximum and minimum points. This shows that more people with all forms of heart disease die during the cold months (+9.6 per cent) than die during the warm summer months (−9.2 per cent).

The results for deaths due to coronary heart disease follow a similar pattern. The difference in this instance between the highest and lowest values amounts to 24.2 per cent.

Since more deaths due to infectious diseases occur during the winter months than in summer months in New York City, it seemed necessary to deduct these deaths from the total deaths due to all other causes. The largest number dying from infectious diseases are in the pneumonia group. These were then deducted with comparisons being made before and after these deductions. It will be noted that such removal does not change the relationship appreciably (Fig. 2).

Thus, it becomes apparent that all forms of heart disease and coronary disease exhibit a seasonal variation above and below that shown by deaths due to all other causes. Furthermore, the peaks occur in the winter months of December and January, with the low points in July and August.

The next step was a correlation of environmental factors which might follow a similar pattern. The following factors were studied; in all cases the data were averaged for a similar ten-year period. These factors are: (1) The average monthly temperatures; (2) the difference between the maximum and minimum temperature; and (3) the average monthly relative humidity.

1. It is apparent from the graph (Fig. 3) that the average monthly temperature deviation from the yearly average varies inversely with the deaths due to all forms of heart disease and also to coronary disease alone.

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*The mathematical method, particularly the use of *subordinate relatives*, can be found elsewhere.[4]

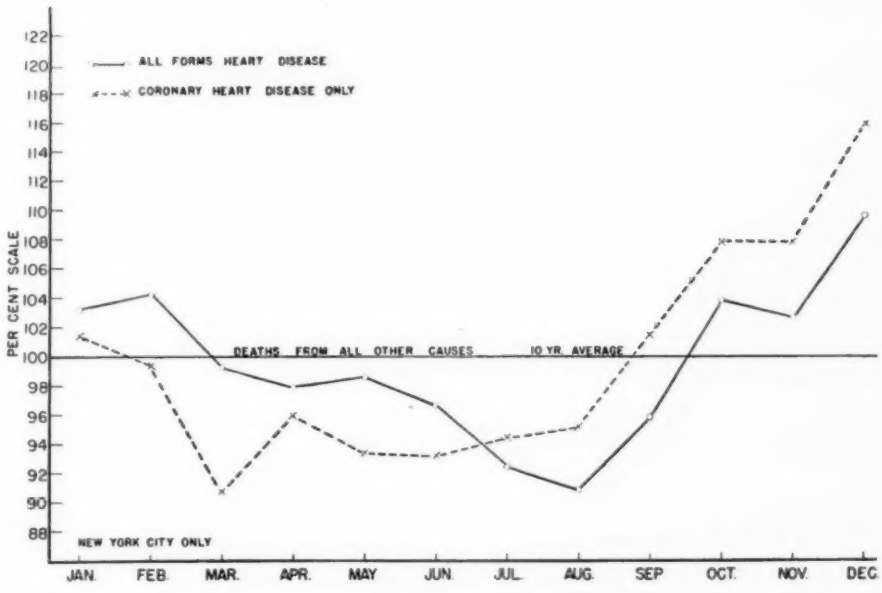
ALL FORMS HEART DISEASE
CORONARY HEART DISEASE ONLY
PER CENT SCALE
DEATHS FROM ALL OTHER CAUSES
10 YR. AVERAGE
NEW YORK CITY ONLY
JAN. FEB. MAR. APR. MAY JUN. JUL. AUG. SEP OCT. NOV. DEC.

Fig. 1.—Changes in heart and coronary disease as related to all other causes.

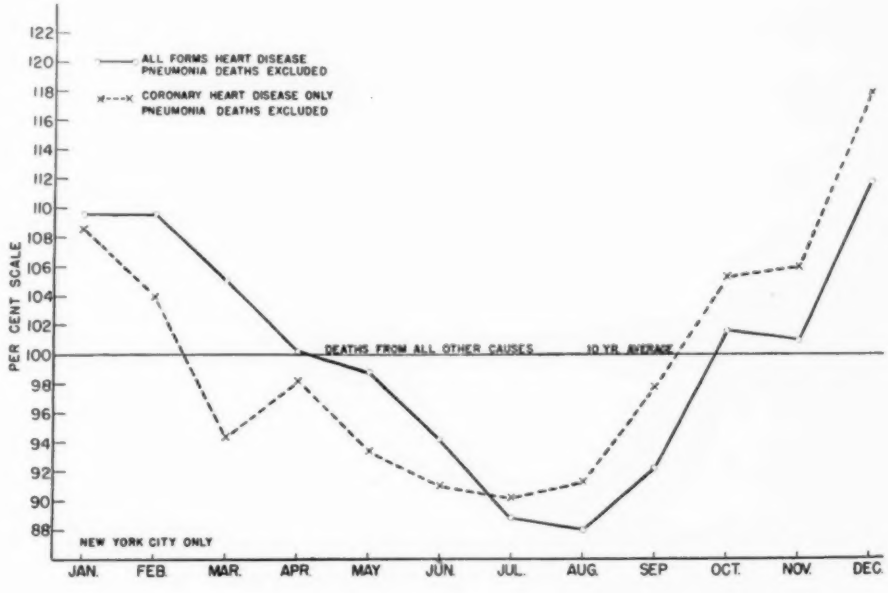
ALL FORMS HEART DISEASE
PNEUMONIA DEATHS EXCLUDED
CORONARY HEART DISEASE ONLY
PNEUMONIA DEATHS EXCLUDED
PER CENT SCALE
DEATHS FROM ALL OTHER CAUSES
10 YR. AVERAGE
NEW YORK CITY ONLY
JAN. FEB. MAR. APR. MAY JUN. JUL. AUG. SEP OCT. NOV. DEC.

Fig. 2.—Changes in heart and coronary disease as related to all other causes (pneumonia deaths deducted).

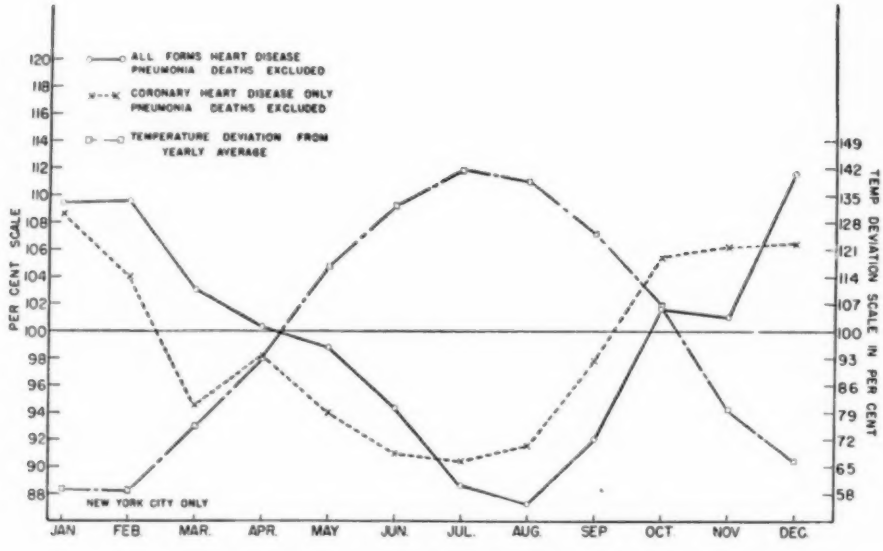
ALL FORMS HEART DISEASE
PNEUMONIA DEATHS EXCLUDED
CORONARY HEART DISEASE ONLY
PNEUMONIA DEATHS EXCLUDED
TEMPERATURE DEVIATION FROM
YEARLY AVERAGE
PER CENT SCALE
TEMP DEVIATION SCALE IN PER CENT
NEW YORK CITY ONLY
JAN. FEB. MAR. APR. MAY JUN. JUL. AUG. SEP OCT. NOV DEC.

Fig. 3.—Mortality changes versus average monthly temperature deviation.

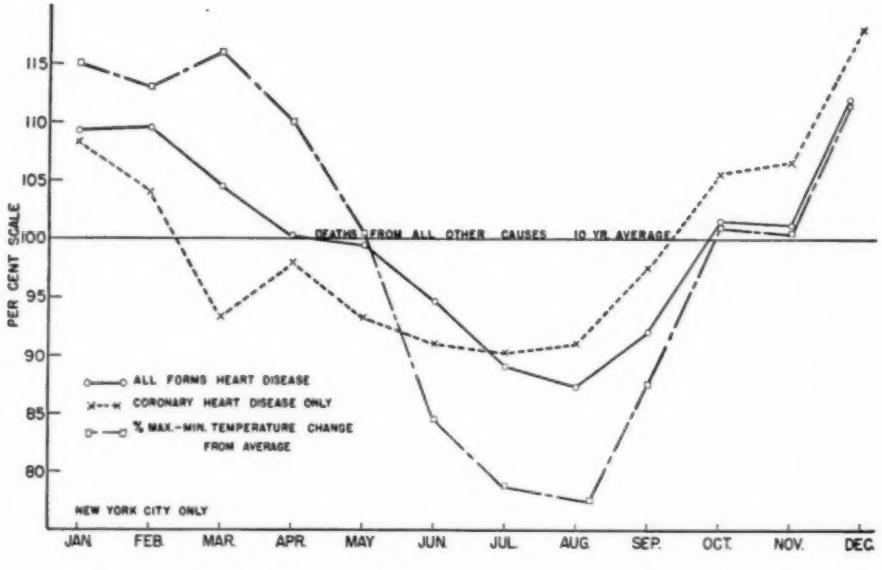
PER CENT SCALE
DEATHS FROM ALL OTHER CAUSES 10 YR. AVERAGE
ALL FORMS HEART DISEASE
CORONARY HEART DISEASE ONLY
% MAX.-MIN. TEMPERATURE CHANGE
FROM AVERAGE
NEW YORK CITY ONLY
JAN. FEB. MAR. APR. MAY JUN. JUL. AUG. SEP. OCT. NOV. DEC.

Fig. 4.—Mortality changes versus maximum-minimum temperature deviation.

2. The maximum and minimum temperature difference curve shown in Fig. 4 follows almost exactly the graphs showing the changes in deaths due to all forms of heart disease and to coronary disease.

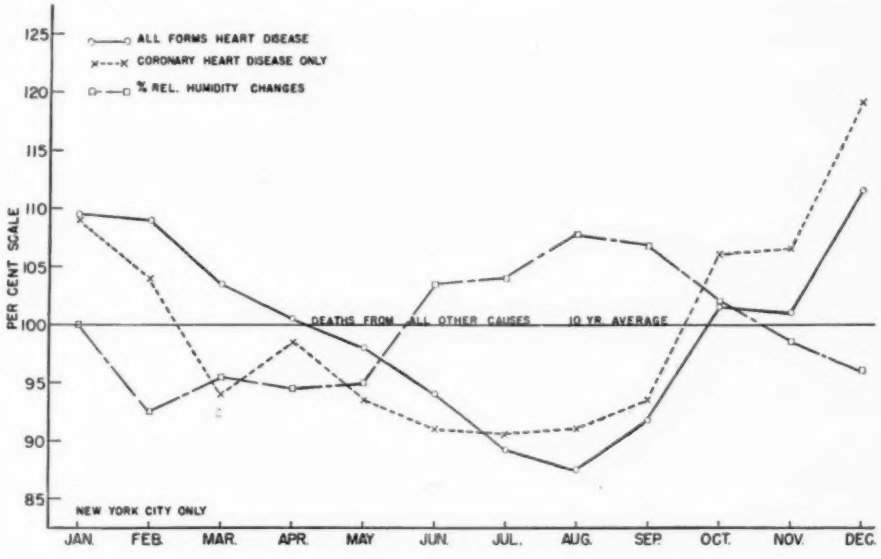

Fig. 5.—Mortality changes versus deviation in relative humidity.

3. The curve of change in relative humidity (Fig. 5) does not follow those of deaths due to heart disease or coronary disease. Thus, one may conclude that relative humidity as it occurs, on the average, in the locale studied bears no direct relationship to the changes in death rates of heart and coronary disease. It is to be noted that the changes which occur in relative humidity cover but an over-all 15 per cent change, whereas the over-all temperature changes in Fig. 3 represent an 84 per cent change. Such a lack of relationship does not necessarily apply to extreme ranges of humidity where extensive humidity changes have been correlated with their effect on heart disease patients. This, in effect, then, should not be construed as contradicting the observations of Burch[3] and others who made their studies in subtropical areas where the humidity ranges are more extreme.

CONCLUSIONS

1. No statement of the accuracy or inaccuracy of diagnoses entered on death certificates can be estimated from a study of mortality statistics gathered in New York City. However, the large volume of cases analyzed tends to reduce the significance of individual diagnostic error and makes this material more valid for statistical study.

2. The removal of seasonal variation from all other causes of death, correction for population changes, and effects due to the seasonal incidence of pneumonia add significance to the changes obtained.

3. A difference of 18.8 per cent was found between the maximum number of deaths occurring in December and the low in August for deaths from all types of heart disease.

4. For coronary disease, the magnitude of change was 24.2 per cent.

5. Even after pneumonia deaths are deducted, the relative changes are the same.

6. The average monthly temperature varies inversely with the changes found in deaths due to all forms of heart disease and to coronary disease.

7. Relative humidity in the locale studied does not follow the changes in death rates of heart and coronary disease.

8. The curve of variation in average differences in the maximum and minimum temperature follows closely that for deaths due to all forms of heart disease and coronary disease.

The authors wish to express appreciation to Dr. William S. McCann for his criticism and suggestions in the review of this manuscript.

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A NOTE ON THE IMPORTANCE OF PROPER TECHNIQUE IN THE RECORDING OF THE PRECORDIAL ELECTROCARDIOGRAM

The Description of an Important Source of Error

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IN AN unpublished study of the electrocardiograms of normal infants and children the ventricular deflections in the precordial leads were found to be of a configuration which could not be satisfactorily explained on the basis of either the position of the heart in the thorax or the presence of unilateral ventricular hypertrophy. It was thought that this supposedly characteristic pattern of the precordial leads was probably the result of distortion of the "true" pattern because of an error in the technique of recording the precordial electrocardiogram, the error consisting of establishing electrical continuity over the surface of the precordium by failing to isolate each of the multiple leads placed close together on a small thorax. Because the magnitude of the distortion may be so great, and because the technical error which has apparently been previously undescribed is very likely occurring frequently in other studies of the electrocardiograms of infants and children, it was considered of some importance to make this the subject of an investigation to be reported in the present paper.

Electrocardiograms were recorded from a number of infants and children of various ages with normal hearts and also with various types of heart disease. The records in each case included the three standard extremity leads and two sets of unipolar precordial leads, using the Wilson central terminal as the indifferent electrode. The first set was taken with care to isolate each exploring point electrically with respect to every other point on the surface of the thorax; the second was taken with electrical continuity established over the surface of the precordium by means of the application of an excessive amount of electrode paste not only on but also between the positions for the precordial leads. The exploring positions were carefully marked on the thorax so that they would be identical in each series of precordial leads and care was also taken to maintain the same string sensitivity of the galvanometer for each set.

It was found in this study that electrical continuity between the exploring positions for the precordial leads, produced by the application of an excessive amount of electrode paste, practically always results in gross distortion of the

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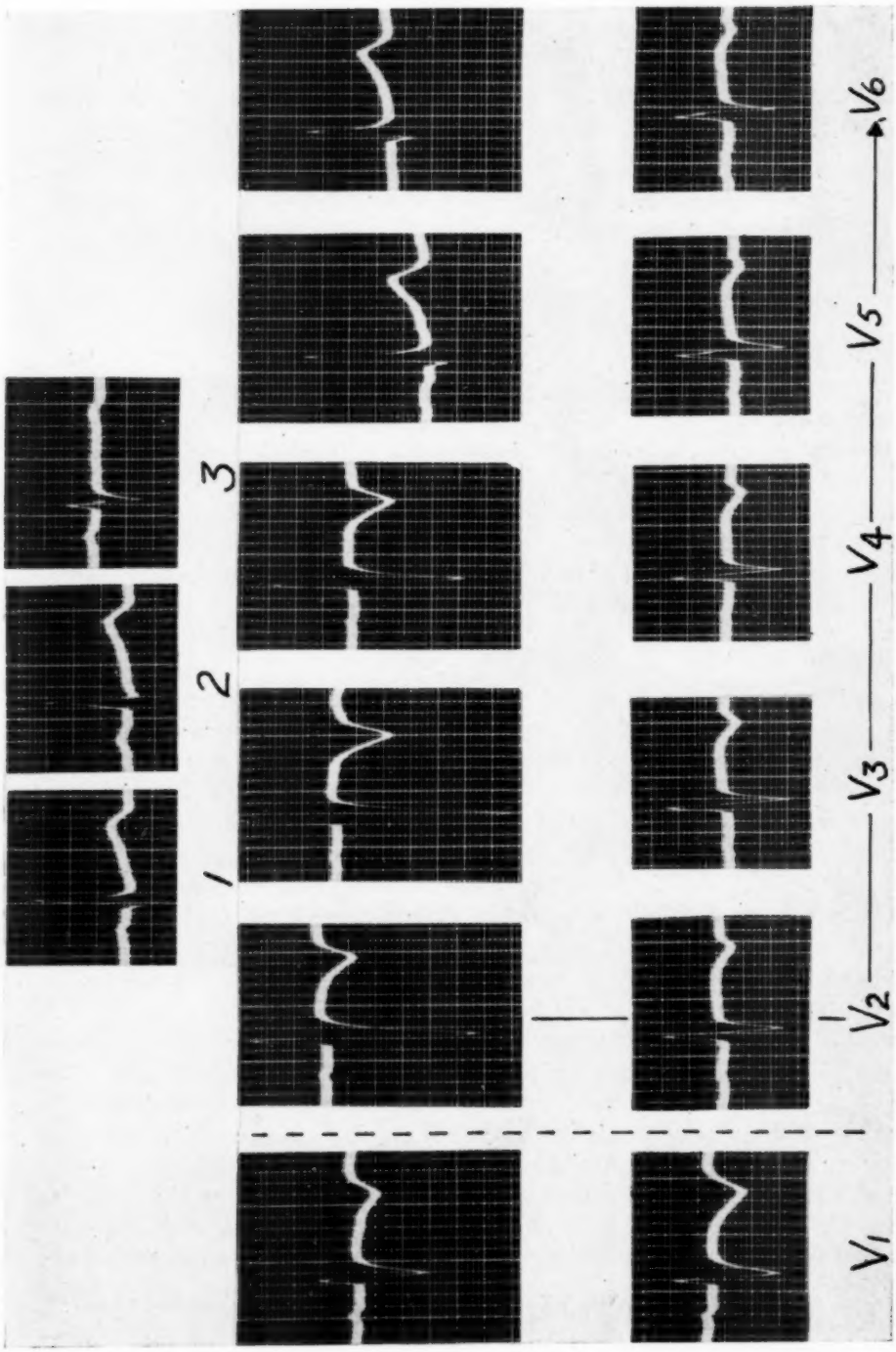

Fig. 1.—R. W., a Negro boy 7 years of age, with sickle-cell anemia and enlarged heart. In this, as in the other illustrations, the upper set of precordial leads is recorded correctly, each position for the exploring electrode being isolated electrically with respect to every other exploring position on the surface of the precordium; the lower set is recorded with surface continuity established between Leads V_2 and V_6 by application of an excessive amount of electrode paste. For further details, see text.

form of the electrocardiogram in these leads. The direction and magnitude of the error appears to depend, to a certain extent at least, on the position of the heart in the thorax and the proximity of certain regions of the heart to the chest wall. Thus, if the predominant potential variations occur in leads from the right side of the precordium, surface conduction will account for distortion of the form of the electrocardiogram in the less dominant leads from the left and mid-precordium. If the predominant potential variations occur in leads from the left side of the precordium, the reverse will be true. There is also some evidence to indicate that conduction and the resulting distortion may occur in more than one direction and from more than one precordial region in the same individual. Examples of the various types of records are given in Figs. 1, 2, and 3.

The first record (Fig. 1) is that of a 7-year-old Negro boy with sickle-cell anemia and an enlarged heart. It is apparent that while there is a distinct transition zone between the ventricular deflections in leads from one side of the precordium as compared with those from the other side (V_{1-4} and V_{5-6}) when recorded correctly, the two types of complexes lose their identity when recorded with the incorrect technique described. Specifically, the conduction effect over the surface of the precordium in this case resulted in (1) a reduction in the amplitude of all of the deflections in the leads between which surface continuity was established, (2) similarity of the configuration of the ventricular deflections in each of these precordial leads, (3) inversion of the T waves in leads from the left as well as in those from the right side of the precordium, and (4) disappearance of Q waves in leads from the left side of the precordium. The predominant electrical effect appears to be originating on the right side of the precordium and is transmitted laterally from right to left. Changes of a somewhat similar type are observed in the precordial leads of the second child (Fig. 2), a 13-year-old white girl with an interauricular septal defect, marked cardiac enlargement, and right bundle branch block. In this instance, however, the predominant electrical effect appears to be originating from the left side of the precordium and is transmitted medially from left to right. The third record (Fig. 3) is that of a 14-month-old white boy with a normal heart. In this case there is evidence of surface conduction in both directions, the T waves becoming upright in Lead V_2 (left-to-right effect) and the Q waves becoming significantly smaller and the S waves larger in Leads V_5 and V_6 (right-to-left effect). Explanation of these changes on the basis of the position of the heart in the thorax would not be simple, and it is probably sufficient for all practical purposes just to emphasize the fact that such changes may occur.

It is apparent that a very considerable error may result from careless technique in recording the precordial leads of the electrocardiogram, particularly in infants and children. It is also apparent that the type as well as the magnitude of the error may have great practical significance both clinically and academically. The direction of the T waves in each of the precordial leads, for example, could have an important bearing upon the determination of the presence or absence of myocardial involvement in acute rheumatic fever and in other diseases in which cardiac damage may occur. Similarly, the relationship of the amplitude

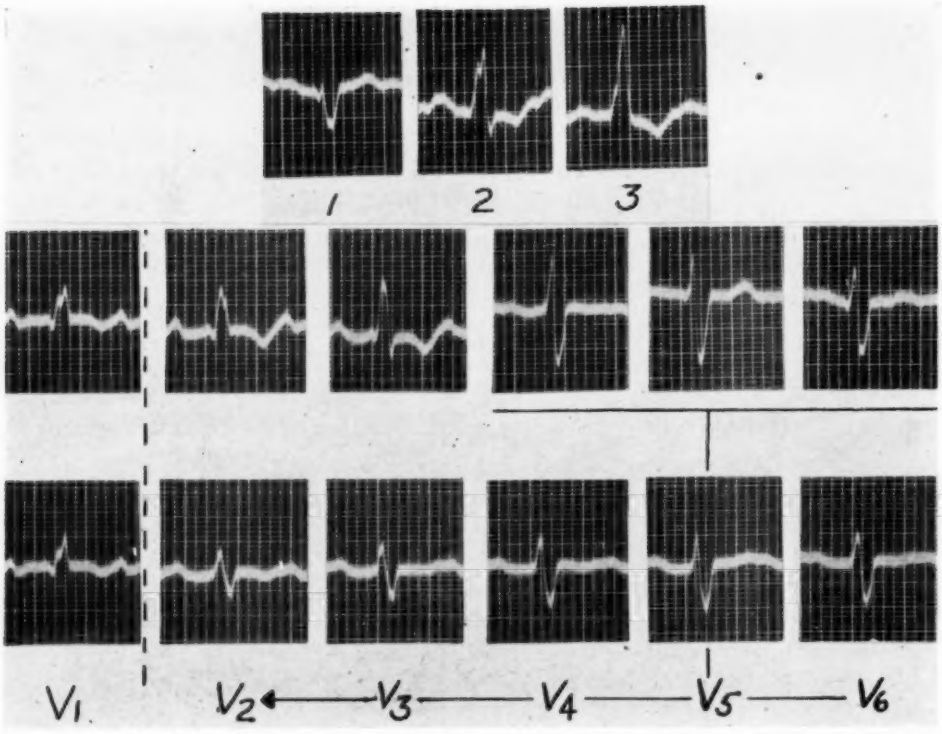

Fig. 2.—M. L., a white girl 13 years of age, with interauricular septal defect, enlarged heart, and right bundle branch block. For details, see text.

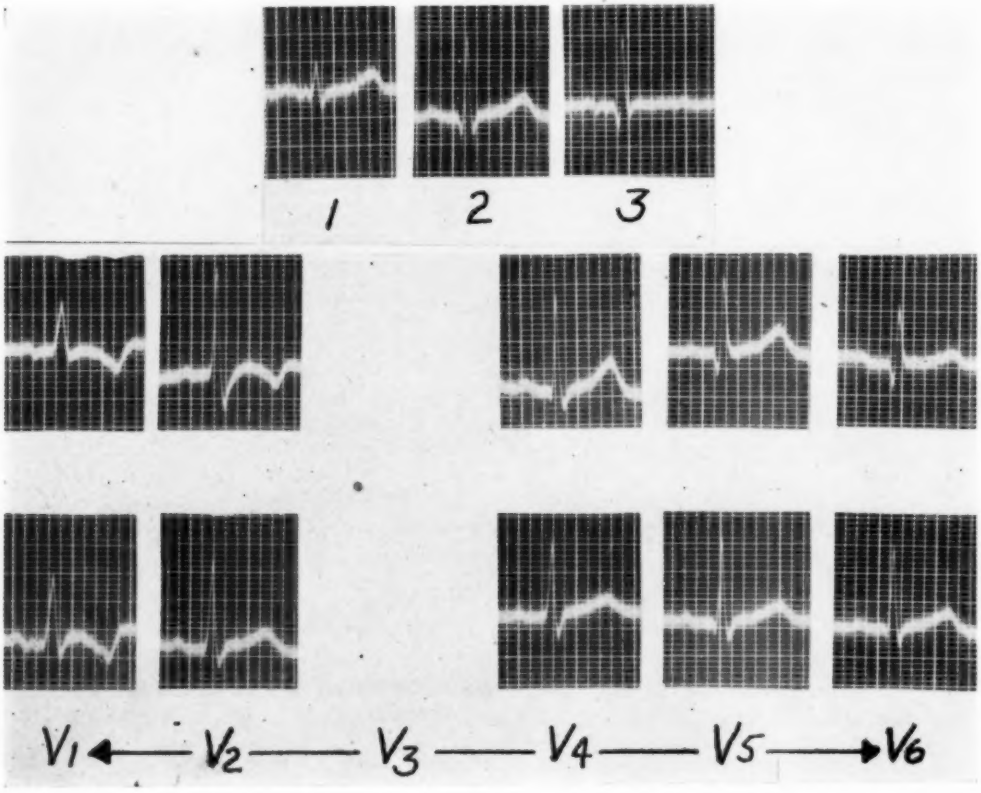

Fig. 3.—R. M., a white boy 14 months of age, with a normal heart. For details, see text.

of the main deflections of QRS in each of the precordial leads may be of importance in the detection of relative hypertrophy of one or the other ventricle. The presence or absence of Q waves in leads from the left side of the precordium will undoubtedly be of significance, particularly when knowledge of electrical events responsible for this deflection is more nearly complete.

The technical error described is not as easily made in adults in whom the distance between the positions for the precordial leads is greater than in infants and small children. It may be avoided in infants and children by (1) application of the electrode paste with care to avoid establishing surface continuity between each of the exploring leads and (2) taking fewer than six precordial leads. A convenient and useful set of precordial leads in infants and children is V_1, V_2, V_4, and V_6, since Lead V_3 is practically overlapped by Leads V_2 and V_4 and Lead V_5 usually closely resembles Lead V_6.

SUMMARY

The value of electrocardiography, as of any other laboratory method, may be limited by errors resulting from faulty technique as well as by errors of interpretation. One such error of technique which has been found to exert a profound effect on the form of the electrocardiogram in the precordial leads consists of the application of an excessive amount of electrode paste not only on but also between the positions for the exploring leads and results in distortion of the "true" precordial potential variations by surface conduction between the various points. This may be avoided by careful application of electrode paste so as not to establish surface continuity between the exploring leads. It is to be emphasized that the type of error described may be of great clinical and academic importance in the interpretation of the electrocardiograms of infants and children particularly.

OBSERVATIONS ON THE EFFECTS ON THE LUNGS OF RESPIRATORY AIR FLOW RESISTANCE IN DOGS WITH SPECIAL REFERENCE TO VAGOTOMY

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THE occurrence of pulmonary congestion, edema, atelectasis, and hemorrhage, after bilateral cervical vagotomy in experimental animals and in the presence of various types of cranial injury and brainstem damage in man, has stimulated numerous investigations on the mechanisms of these effects. Recent papers by Farber[2,3] and by Short[7] review much of the relevant literature and it will not, therefore, be analyzed at this time, except with regard to papers bearing directly on the observations to be reported. This paper will deal solely with pulmonary lesions seen after long periods of spontaneous breathing against inspiratory and expiratory resistances by anesthetized dogs, with and without bilateral cervical vagotomy.

These experiments were undertaken in order to give answers to several simple questions. The first question is whether a drastic increase in the negative intrathoracic pressure will, by itself, cause lung edema. This point is important because Lorber[5] and others have ascribed an important role to airway obstruction in the genesis of lung edema after vagotomy. The general logic is that lowered intrapulmonic and intrathoracic pressures may favor ultrafiltration from the capillaries by increasing the pressure gradient between the capillaries and the extravascular spaces. Implicit in this reasoning is the untested assumption that pulmonary capillary pressure does not fall exactly in proportion to the intrathoracic pressure.

The second question is whether bilateral vagotomy may influence the course of events after the negative intrathoracic pressure has been made to increase. It seemed possible that the pulmonary vasodilatation after vagotomy, to which Farber[4] ascribes a determining role in causing lung edema after vagotomy, might aggravate the pulmonary pathology caused by inspiratory resistance.

The third question is whether increasing the positive pressure in the chest by setting up an expiratory resistance might reverse the processes seen with inspiratory resistance.

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Received for publication June 23, 1947.

METHODS

Mongrel dogs were anesthetized with nembutal, 30 mg. per kilogram of body weight, administered intraperitoneally, without other medication. Tracheotomy was performed and the largest sized glass cannula, ranging from 1.0 to 1.6 cm., which could be inserted was fixed in place. The cannula was attached to 8.0 mm. glass tubing leading at a distance of 15 to 17 cm. to a T-tube connecting two valves. One valve was an A 14 Army Air Force Oxygen Mask one-way valve, directed to give free flow in either inspiration or expiration for the two types of experiments; the other was a fluid level valve arranged, in one case, for flow against resistance in inspiration and in the other, in expiration. The valves are diagrammed in Fig. 1. The dead air space is that between the trachea and the T-tube. The volume of dead air is less than that of the larynx, pharynx, and nose or mouth.

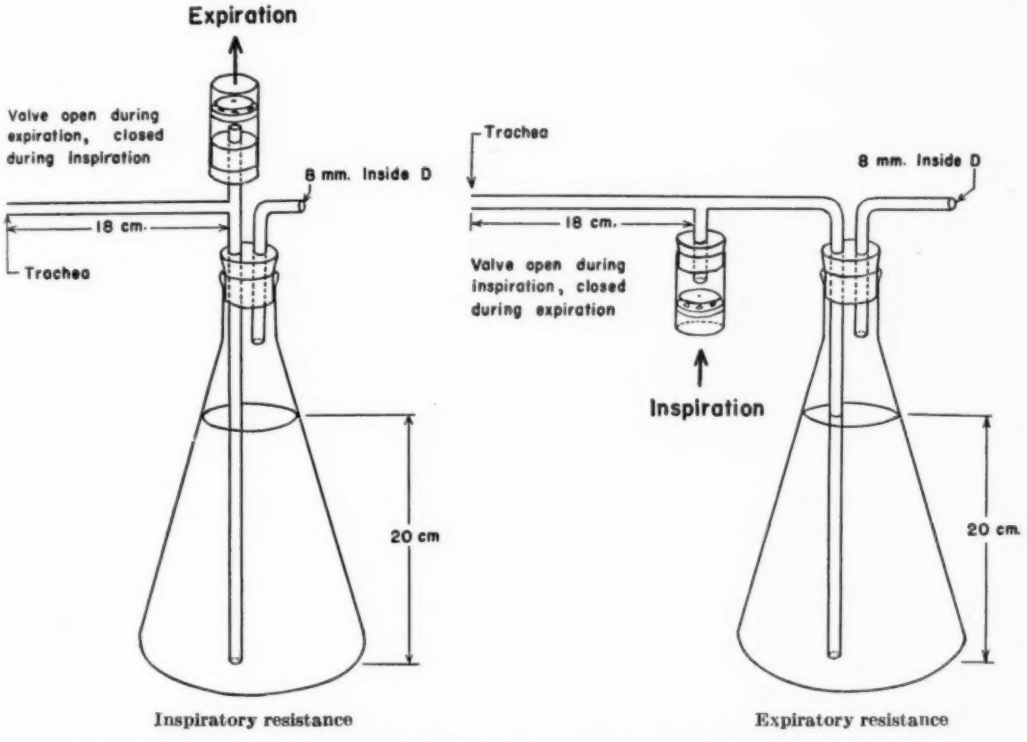

Fig. 1.—Diagrams of arrangement for imposing airway resistance in inspiration or expiration.

The animals were allowed to breathe room air at their own spontaneous rhythm against either an inspiratory or an expiration resistance of 20 cm. H_2O, or, in a few instances as indicated, without resistance. In the instances so designated, the vagus nerves were cut in the midcervical region.

In prolonged experiments, additional amounts of nembutal were administered in quantities just sufficient to prevent struggle. The doses are indicated in the report of results.

Attempts were made to quantitate by various methods the degree of damage to the lung by the procedures employed. Lung weight-body weight ratios were measured and abandoned as criteria because of the normal variability and because of the lack of correlation with obvious pathology. The lung weight-heart weight ratio was abandoned for the same reasons. Evidently unselected mongrel dogs show such great normal variability with respect to these ratios as to make them meaningless until very gross changes have occurred. Measurements of changes in volume elasticity were also attempted and abandoned because of technical difficulties, although it is believed that this method is possible if all important variables can be taken into account.

It was decided to quantitate the results of the experimental procedures in this study by evaluation of the gross and microscopic appearance of the lungs, taking into account the presence or absence of areas of lung which failed to collapse upon opening the chest and which showed congestion with blood. Samples of tissues were studied in microscopic section for evidences of edema, congestion, and hemorrhage.* Admittedly subjective factors enter into these evaluations. However, we are convinced that at the present time the gross and microscopic observations provide the most reliable criteria of lung pathology available. Photographic reproductions of lesions will not be presented because they were entirely typical.

RESULTS

The results of experiments on thirty-six animals are shown in Table I. The large number of experiments was resorted to because of the variability of the results. Several facts are evident upon inspection of the data. The survival times in animals which were allowed to live as long as they would, in the inspiratory resistance group of thirteen dogs, varied from five to forty-nine hours. One animal survived seventy-two hours and was sacrificed. The long survival times suggest that some dogs are remarkably resistant to the damaging effects of great lowering of the intrathoracic pressure in inspiration. However, in nine of eleven dogs with intact vagi that were allowed to die in these experiments, there was moderate to massive lung edema and congestion. Further, in those sacrificed there were, in four out of five instances, minimal to marked pathologic changes. In the five vagotomized animals, three of which were sacrificed and two of which died spontaneously, there were also congestion and edema, but of minimal to moderate degree, involving only the dependent portions of the lungs. In general, it can be said with assurance that vagotomy was not followed by more severe lung changes. The surprising result of these experiments was the fact that dogs could breathe so long with such low intrathoracic pressures as are required with a 20 cm. H_2O inspiratory resistance, and show so little lung change, particularly in the vagotomy series.

In the expiratory resistance group with intact vagi, four of five animals dying spontaneously showed lung lesions ranging in degree from minimal to

*We are indebted to the Department of Pathology and to Dr. Karl E. Karlson for assistance in the microscopic studies.

massive, and in the two sacrificed before death, the changes were moderate to severe. With expiratory resistance and bilateral vagotomy, the lesions were absent in one animal and minimal in two others. Thus, the vagotomized dogs showed less damage than did those with intact vagi. In fact, the vagotomized experimental animals showed lesions comparable to the minimal ones seen in tracheotomized, anesthetized dogs subjected to no experimental procedures and sacrificed at seven or eight hours, with or without vagotomy.

TABLE I. TABULATION OF RESULTS OF INDIVIDUAL EXPERIMENTS

WEIGHT	INITIAL‡ DOSE (MG.)	TOTAL‡ DOSE (MG.)	POSITION	RESISTANCE	VAGOTOMY	SURVIVAL (HR.)	LUNG PATHOLOGY§
17.9 ♂	325	1200	Supine	Inspiratory	−	13:30 d*	2
25.2 ♀	750	2800	Supine	Inspiratory	−	48:50 d	3
7.3 ♂	200	350	Supine	Inspiratory	−	7:35 d	2
11.8 ♀	250	1100	Supine	Inspiratory	−	17:45 d	4
10.2 ♂	300	600	Supine	Inspiratory	−	5:00 d	3
11.1 ♂	450	875	Supine	Inspiratory	−	7:00 d	4
10.7 ♂	350	650	Supine	Inspiratory	−	7:00 s†	2–3
13.6 ♀	500	700	Supine	Inspiratory	−	7:15 s	1
13.0 ♂	500	575	Supine	Inspiratory	−	6:30 d	1
13.1 ♀	550	550	Supine	Inspiratory	−	6:30 d	2
17.0 ♂	350	1125	Supine	Inspiratory	−	31:00 d	4
18.1 ♂	400	1750	Supine	Inspiratory	−	32:00 d	1
9.1 ♂	200	750	Supine	Inspiratory	−	17:00 d	2
14.6 ♂	300	2800	Supine	Inspiratory	−	72:00 s	1
10.9 ♀	350	650	Prone	Inspiratory	−	6:15 s	0
10.0 ♀	400	550	Prone	Inspiratory	−	7:25 s	3
21.1 ♂	750	1100	Supine	Inspiratory	+	8:55 d	1–2
22.7 ♀	750	1050	Supine	Inspiratory	+	7:15 d	1–2
14.1 ♀	450	600	Supine	Inspiratory	+	7:10 s	1–2
10.7 ♂	350	450	Supine	Inspiratory	+	7:00 s	1–2
9.5 ♂	550	650	Prone	Inspiratory	+	7:00 s	1–2
30.7 ♂	1000	1500	Supine	None	−	7:15 s	0–1
14.1 ♂	500	750	Supine	None	−	7:15 s	0–1
8.4 ♂	300	500	Prone	None	−	7:10 s	0–1
14.8 ♂	500	1000	Supine	None	+	8:15 s	0
9.5 ♀	300	500	Prone	None	+	7:30 s	0–1
7.7 ♀	300	375	Supine	Expiratory	−	1:30 d	1
10.7 ♂	400	600	Supine	Expiratory	−	7:15 d	1
15.5 ♀	500	950	Supine	Expiratory	−	7:15 s	2
11.4 ♀	375	550	Supine	Expiratory	−	8:00 d	4
15.4 ♀	450	2050	Supine	Expiratory	−	62:00 d	3
16.0 ♂	500	850	Supine	Expiratory	−	14:00 d	0
15.5 ♂	500	700	Supine	Expiratory	−	7:15 s	2–3
8.4 ♀	300	450	Supine	Expiratory	+	4:00 d	0–1
13.9 ♀	500	700	Supine	Expiratory	+	7:00 s	0
10.9 ♂	400	550	Supine	Expiratory	+	7:15 s	0–1

*d = died. †s = sacrificed. ‡ Nembutal.
§1, Slight congestion and edema involving the dependent portions of the lungs.
2, Moderate congestion and edema involving the dependent portions of the lungs.
3, Marked congestion and edema involving the dependent portions of the lungs.
4, Frank hemorrhage, congestion, and edema involving all the lobes of the lung.

Most of these experiments were performed with the animal lying supine. A few were done in the prone position but no remarkable difference was seen between the two postures; therefore, the results are treated together.

The observations on dogs sacrificed at six or eight hours are believed to be most significant as regards comparison of pulmonary pathology. The data obtained on survival with respiratory resistances are presented, however, because the variability in survival time and extent of lung lesion are believed to be important to an evaluation of the data presented here and by other authors.

The results of all types of experiments are summarized in Table II, in which a mean Index of Lung Pathology for each group is calculated. These indices show clearly that bilateral cervical vagotomy did not, in these experiments, increase the degree of lung damage. In fact, the trend is in the opposite direction, although the relatively small number of experiments prevents one from ascribing significance to the difference.

TABLE II. SUMMARY OF RESULTS OF ALL TYPES OF EXPERIMENTS

NO. OF ANIMALS	RESISTANCE	CONDITION OF VAGUS	DEATH	INDEX OF LUNG PATHOLOGY
5	Insp.	Intact	Sacrifice	1.5
3	Insp.	Cut		1.5
2	Exp.	Intact		2.3
2	Exp.	Cut		0.3
3	None	Intact		0.5
2	None	Cut		0.3
11	Insp.	Intact	Spontaneous	2.5
2	Insp.	Cut		1.5
5	Exp.	Intact		1.8
1	Exp.	Cut		0.5

DISCUSSION

It is rather surprising that either inspiratory or expiratory air flow resistance should cause varying degrees of pulmonary edema, congestion, and hemorrhage in dogs. It might have been supposed that since one causes increased negative pressure and the other, increased positive pressure in the thorax, the results might be opposite in the two cases. The failure to find such a contrast can only mean, it seems, that in one or both cases the end results are mediated quite indirectly, through mechanisms other than the direct effects of the pressures on normal pulmonary tissues and blood vessels. A search of the literature has not provided information adequate to trace such mechanisms.

Moore and Binger[6] studied six dogs with inspiratory resistance and four with expiratory resistance for short periods of time, obtaining congestion and edema in the first group and no regular change in the second. Carr and Essex[1] investigated certain effects of positive pressure breathing in dogs, under conditions different from those employed in this study.

Since the imposition of resistance to air flow in either inspiration or expiration in dogs was followed by pathologic changes in the lungs it seemed logical to suppose that, if vagotomy predisposed the dog to pulmonary edema, one should find an increase in edema following vagus section under such circum-

stances. The failure to observe it does not, however, preclude the possibility that under other circumstances vagotomy might favor the production of lung edema. The observations presented here do, however, seem to prove that cervical vagus section does not favor lung edema under all circumstances.

Lung edema, congestion, and hemorrhage depend for their production on multiple factors, such as the pulmonary capillary pressure, the physicochemical and physical state of the capillary wall, the pulmonary tissue pressure, and perhaps others. Each of these immediate determinants probably depends on several secondary factors. Hypoxia possibly plays a role in the genesis of lung lesions in these experiments. It is, however, impossible with available information to determine which factors are related causally. Attempts to generalize in this problem would be premature at the present time. What appears to be needed is more specific information about the important variables under controlled conditions.

One consistent incidental observation not mentioned under the section on results was that dogs with intact vagi were more strained by 20 cm. H_2O airway resistance than were the vagotomized animals. The slower and deeper respiration after vagotomy may be an important factor in this connection. In a number of instances, resistance breathing was established and vagotomy performed shortly thereafter. In these cases the breathing became more regular and more quiet after vagus section.

CONCLUSIONS

1. When dogs anesthetized with nembutal were made to breathe against an airway resistance of 20 cm. H_2O during either inspiration or expiration, significant degrees of pulmonary edema, congestion, and hemorrhage were observed upon sacrifice at six to eight hours, or at the time of spontaneous death.

2. Bilateral cervical vagotomy did not increase the tendency to lung edema under these circumstances.

3. Pulmonary lesions after resistance breathing appear to depend upon multiple factors and cannot at present be accounted for in terms of simple direct effects of pressure upon the pulmonary tissues and vascular bed. An analysis of actual mechanisms awaits acquisition of additional factual data.

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MEASUREMENT OF THE TOTAL TRANSVERSE DIAMETER OF THE HEART BY DIRECT PERCUSSION

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THERE has been for many years much debate about the value of percussion in determining heart size. This study was undertaken in the hope of obtaining a clearer picture of the probability of error of such determinations, particularly in regard to the total transverse diameter of the heart compared with measurements on teleroentgenograms.

The material for the study consists of a review of the case histories of all private patients examined by the senior author in his office during the year 1945. Some of these patients had been examined at intervals over a period of years. All case histories were included in which at least one teleroentgenogram and independent heart outline measurements by percussion had been made. If several such examinations had been made, they were included. No cases were included in which roentgenographic measurements had been reported prior to examination.

On the day of the office visit, the patient went to the Pennsylvania Hospital for a teleroentgenogram. These films were made in deep inspiration with the patient in the erect position; the target-film distance was 6.0 feet and the exposure time was 1/8 second. The report included a pencilled tracing of the heart and chest outlines, the measurement of the maximum distance in centimeters of the right and left heart borders from the midline, and the total transverse diameter of the heart. The latter measurement was compared with the predicted total transverse diameter, as estimated on the table prepared by Hodges and Eyster.[1]

Shortly after the six-foot film was made and before it was reported, the patient received a physical examination. The borders of the heart were percussed with the patient's chest vertical; the right heart border in the fourth intercostal space, the left in the fifth. The percussion was accomplished by direct rather than indirect percussion. The stroke was made lightly and evenly by the pad of the middle finger of the right hand against the chest wall, starting at a point well outside the probable limit of dullness and percussing toward the midline (Figs. 1 and 2).

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Before presenting our results, it would be well to discuss some of the factors and probable errors involved in measurement of heart size by teleroentgenograms and percussion.

Due to the divergence of the roentgen beam, the image on a roentgen film is always distorted as to size. This is minimized by increasing the target-film distance to six feet, but since the heart is not in contact with the film, distortion cannot be entirely eliminated. The image of an object three inches from the film is increased 4.35 per cent at six foot target-film distance, while an object eight inches from the film will be distorted 12.5 per cent. In a fat woman with large breasts, this latter circumstance may be approached.

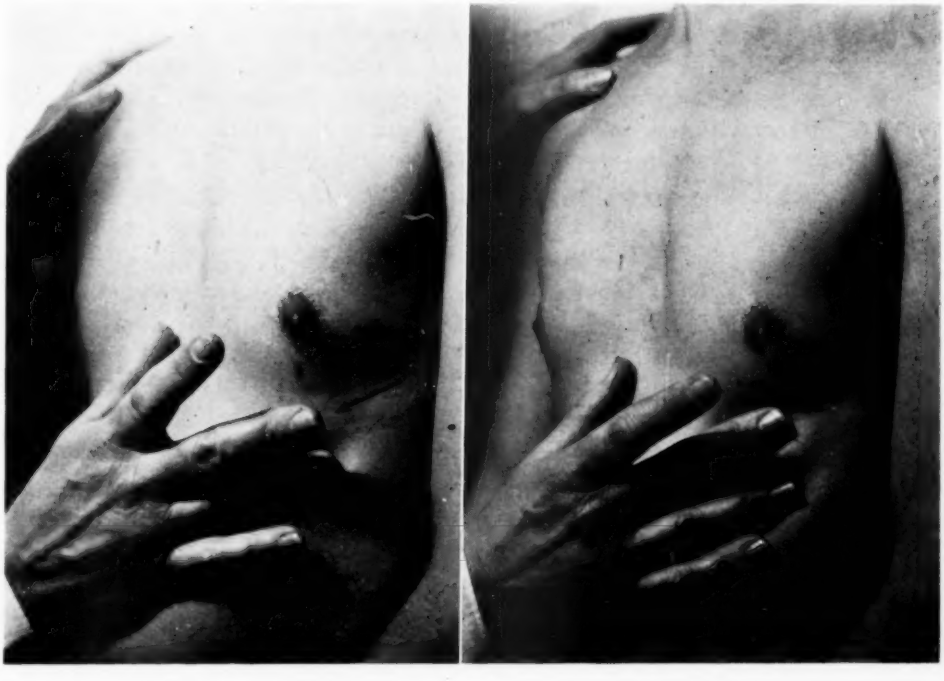

Fig. 1. Fig. 2.

Figs. 1 and 2.—Method of percussion. Arrow indicates percussing finger.

The heart shadow varies in size depending on whether the heart is in systole or diastole. The inability to obtain a film in which the heart cycle is identical in all exposures causes some deviations in heart size. The exposure of 1/8 second only covers a small fraction of the cardiac cycle. In a vigorously beating heart, the transverse diameter of the heart may vary 1.0 to 2.0 cm. between systole and diastole; this causes additional error.

The extra-cardiac fat pad, when present, may be misleading and must be discounted in making measurements on the film. Otherwise, the left heart border will be measured outside its true border.

The tables of Hodges and Eyster or any other formula for prediction of heart size are subject to some error if the patient has had a recent sudden change of weight, if the abdomen is distended with fluid or by a pregnant uterus, and, in some patients, if the abdomen is relaxed.

As for percussion measurements, the first point of importance is to review the depth of the heart borders from the anterior chest wall. The left heart border normally lies in close approximation to the chest wall, but there is a thin layer of lung tissue between which disappears a short distance from the left sternal border. This relationship varies slightly with the respiration and the phase of the cardiac cycle. Clearly, it follows that heavy percussion will miss the first faint change in note and that a relatively light stroke is needed. Another significant point is that one is percussing a curved surface, not a flat one. Thus, as one percusses around the left anterior curve of the chest, particularly in the mid to anterior axillary line, cardiac dullness will become apparent before the actual heart border is reached, as one is percussing toward the midline rather than in an anterior-posterior direction. This is of importance mainly in hearts moderately enlarged or displaced to the left.

Those who think that it is impossible to percuss the right cardiac border with sufficient accuracy to make it of value in physical examination believe that one is percussing the right sternal border rather than the right cardiac border. This may be true, except in cases of marked right-sided cardiac enlargement. However, the fact that in our series the total transverse percussion diameters were relatively equal to the total transverse x-ray diameters would indicate that direct percussion of the cardiac diameters is justifiable. It should be emphasized that constant practice in the percussion of cardiac borders, supplemented by correlation with the x-ray measurements, is essential if one is to have reliance in his own percussion measurements.

It is interesting to note that direct percussion of the left border gives almost universally larger figures than the x-ray diameters of the left border, while the reverse is true of the right cardiac border. This is in accord with the findings of Kurtz and White in a similar study made at the Massachusetts General Hospital. Therefore, in the large majority of examinations, the total transverse cardiac diameters by direct percussion closely approximate the total transverse cardiac diameters given by x-ray.

Realizing that "figures never lie but liars figure," we have prepared as simply as possible four charts of our findings. In Chart I we present the results of 333 comparative measurements in 305 men. In this figure, the columns represent the number of measurements by percussion that are within a certain percentage of the actual x-ray measurements. It will be seen that 74 per cent of the measurements were within plus or minus 10 per cent, while 88 per cent were within plus or minus 15 per cent of the x-ray measurements. The figures would look even better if we realize that three of the five measurements which were 31 per cent larger than the x-ray measurements were done on one man over a period of years and that two of the four measurements that average minus 33 per cent of the x-ray measurements had a similar explanation. As we would

expect from the magnification of the roentgen shadow and the interference to percussion of the overlying lung around the heart margins, 208 percussion measurements were smaller than the x-ray measurements, while only 118 were larger.

In Chart II, the same cases are presented. In this chart is shown the deviation in centimeters rather than per cent; in 58 per cent, the measurements were

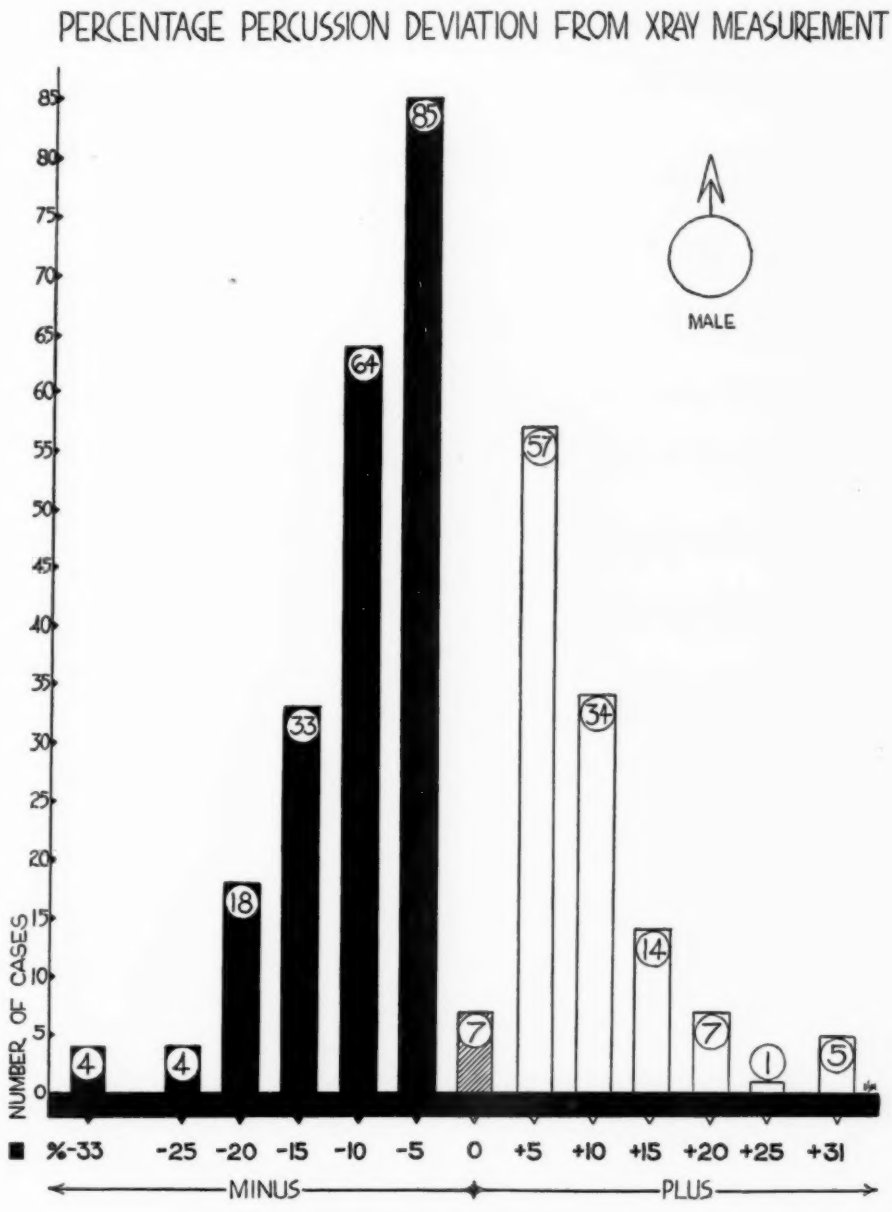

Chart I.

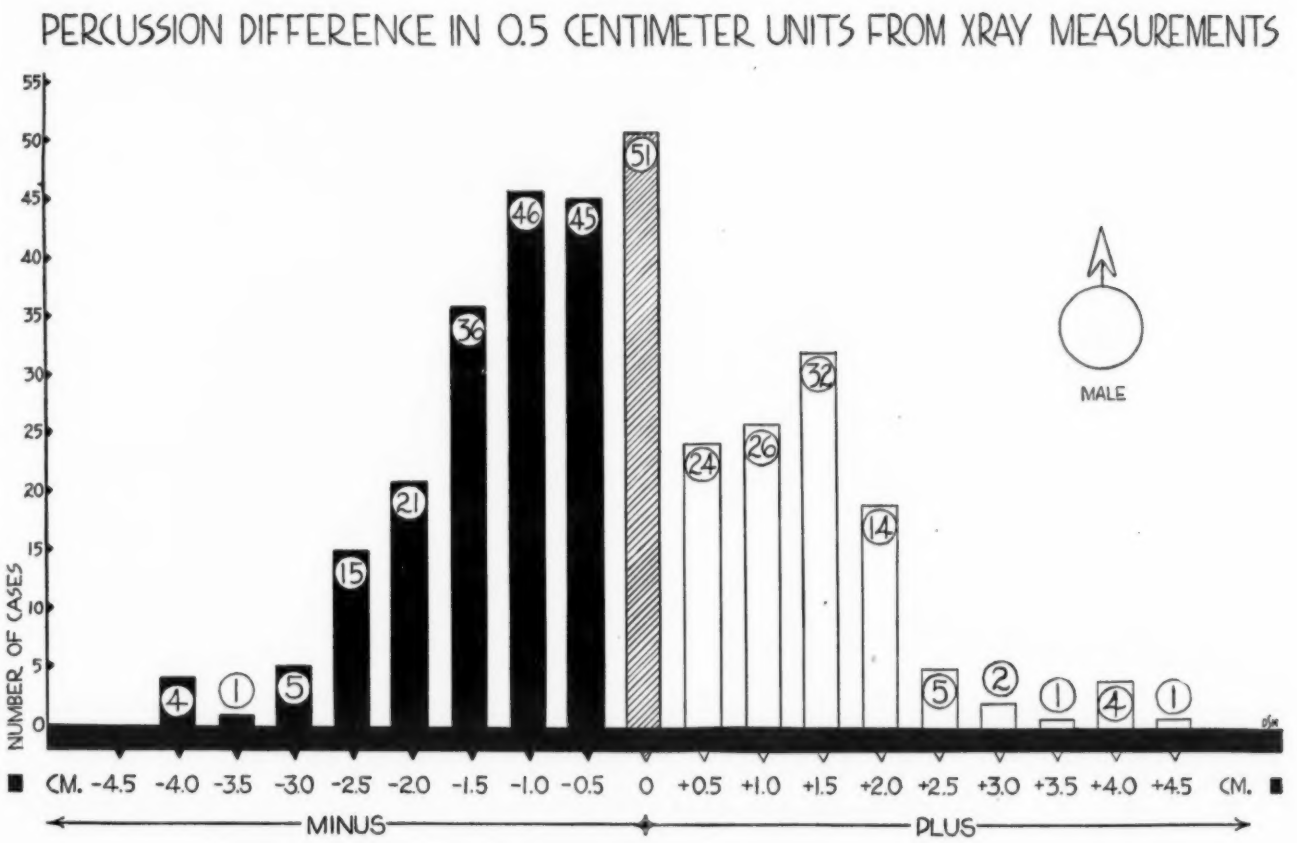
PERCUSSION DIFFERENCE IN 0.5 CENTIMETER UNITS FROM XRAY MEASUREMENTS
NUMBER OF CASES
55
50
45
40
35
30
25
20
15
10
5
0
4
1
5
15
21
36
46
45
51
24
26
32
14
5
2
1
4
1
MALE
CM. -4.5 -4.0 -3.5 -3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0 +0.5 +1.0 +1.5 +2.0 +2.5 +3.0 +3.5 +4.0 +4.5 CM.
MINUS
PLUS

Chart II.

within 1.0 cm. of the x-ray measurements while in 89 per cent they were within 2.0 cm. of the latter. We feel that the figures speak for themselves. Although there are a few measurements in gross error, most are within the normal range of error of the measurements by x-ray.

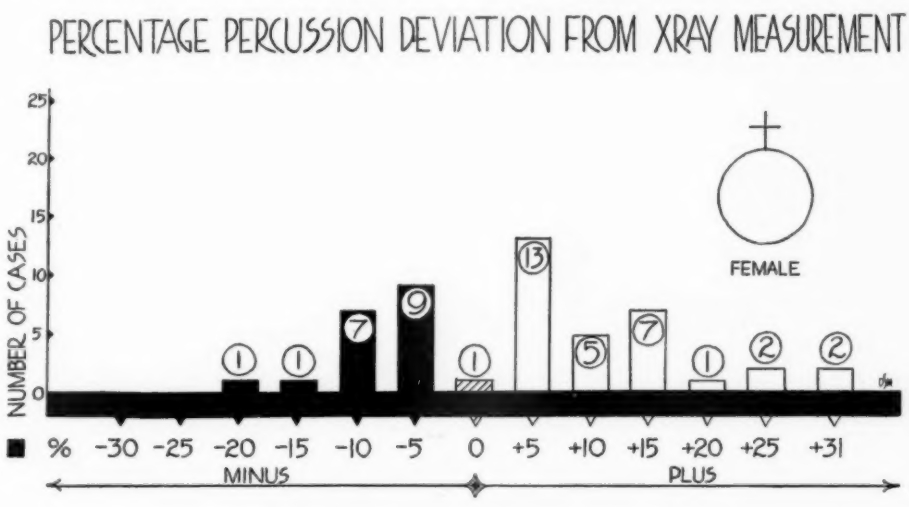

Chart III.

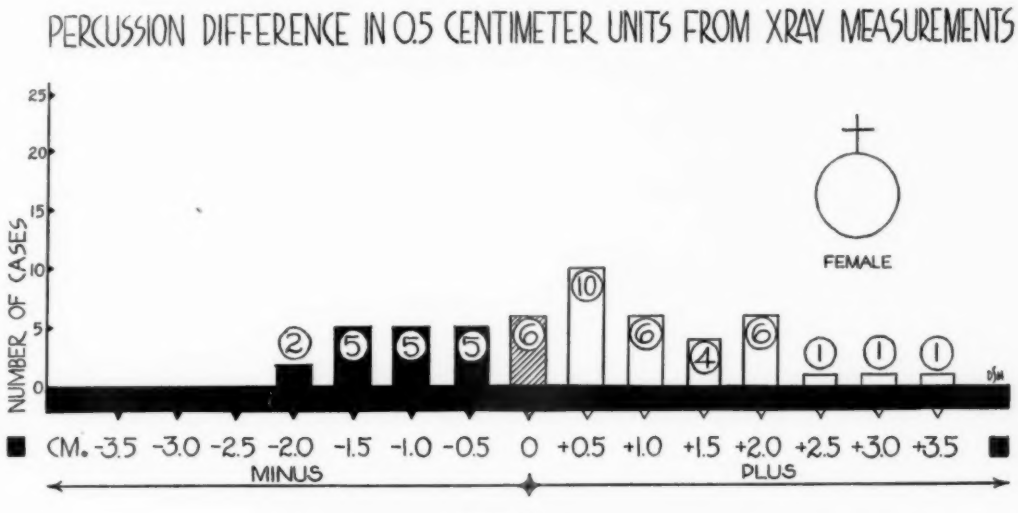

Chart IV.

Although only a few women (forty-five) were percussed, the results are given in Charts III and IV. There were fifty-two examinations. In Chart III (as in Chart I), the percentage of deviation of the percussion measurement from the x-ray measurements is represented; in 64 per cent percussion measurements were within plus or minus 10 per cent of the x-ray measurements and

80 per cent within plus or minus 15 per cent. In Chart IV, the same cases are presented, illustrating the variation to the nearest 0.5 centimeter; 58 per cent were within 1 cm., 90 per cent were within 2.0 centimeters. Interestingly enough, twenty-nine percussion measurements were greater than the x-ray figure, while only seventeen were less. The breast tissue in adult women makes accurate percussion very difficult, but in some, as our findings illustrate, fairly accurate results may be obtained.

From the figures we have presented, it is apparent that direct percussion of the transverse diameters of the heart is of distinct value for the following reasons. If it is difficult or impossible to obtain accurate roentgen measurements, the results are reasonably accurate in predicting the cardiac diameters. It does not cost anything to percuss the heart. It may give more accurate estimation than the x-ray method in cases in which the Hodges and Eyster formula may be in error, as mentioned in the first part of the text. Also, from the standpoint of the consultant, the procedure of direct percussion of the cardiac diameters is most impressive to the patient and the family. It is one procedure in physical examination which the family physician has not performed already!

SUMMARY

1. A study comparing the total transverse cardiac diameters as obtained by direct percussion with the measurements on teleroentgenogram is presented.

2. A discussion of the possible sources of error in both methods of examination is included.

3. Of 333 examinations of 305 men, percussion measurements in 74 per cent were within plus or minus 10 per cent of the teleroentgenographic figures; 88 per cent were within plus or minus 15 per cent. In 58 per cent, percussion figures were within 1.0 cm. of the teleroentgenographic measurements.

4. Fifty-five comparative examinations of forty-five women gave similar results.

5. Direct percussion of the total transverse cardiac diameters appears to be of decided value in men.

The authors are indebted to Dr. Paul A. Bishop, Director of the X-ray Department of the Pennsylvania Hospital, for his helpful criticism of this paper.

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INTENSITY AND DURATION OF ACTION OF QUINIDINE SULFATE IN AURICULAR FIBRILLATION AND FLUTTER

As Measured by the Rate of the Circus Movement

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IN THE treatment of patients with auricular fibrillation by the oral administration of quinidine sulfate, it is common practice to give repeated doses of 0.4 Gm. at intervals of two to four hours. The intensity and duration of such repeated doses has not previously been compared, in the same patient, with that obtained after a single dose of this size or larger. It will become apparent that the results of this comparison have a practical bearing on quinidine therapy.

Lewis and associates[1] found that after a single dose of 0.6 or 0.8 Gm. quinidine sulfate was given to patients with auricular fibrillation, the rate of the circus movement was minimal in from one and one-half to three and one-half hours. The rate remained minimal for an hour, sometimes longer, then began to rise gradually. The effect of such doses was never over in eight hours and rarely over in twenty-four hours. The control rate was always re-established within forty-eight hours. These authors also gave two patients, on different days, single doses of 0.2, 0.4, 0.6 and 0.9 Gm. quinidine sulfate. The circus rate decreased by almost equal increments as the dose increased. It was noted, however, that the fall in the circus rate was not proportional to the dose, and that although the increase from the third to the fourth dose was 0.3 Gm., the corresponding fall was not "proportionately exaggerated."

Wiechmann[2] showed that the amount of quinidine excreted in the urine by human subjects is smaller after a single large dose than when the same amount is given in divided portions over a period of time. Accordingly, he recommended that for therapeutic purposes the largest possible dose compatible with clinical safety be given with the least fractionation.

The observations reported in this paper were made to compare the intensity and duration of the effect on the rate of the circus movement of auricular fibrillation and flutter of single doses (0.4 Gm. and 0.8 Gm.), and of repeated doses (0.4 Gm. every two hours for three or four doses) of quinidine sulfate given orally.

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METHODS

Observations were made on six patients, five with auricular fibrillation and one with auricular flutter. In the patients with auricular fibrillation, the rate of the circus was determined by counting the auricular waves in electrocardiograms recorded by the method suggested by Lewis.[3] Two electrodes were placed on the chest along the right sternal border at sites chosen to yield maximal deflections. Their location varied slightly in different patients but was kept constant in each case throughout the period of study. In the patient with auricular flutter the rates were counted in tracings taken with the usual limb leads. The five patients with fibrillation were fully digitalized first, then kept on a maintenance dose of digitalis while the studies were in progress. No digitalis was given to the patient with flutter.

Each patient received a preliminary test dose of 0.2 Gm. quinidine sulfate to screen out patients with idiosyncrasy to the drug. Three or four days later, after a control electrocardiogram had been taken, the first full dose of quinidine was given. Electrocardiograms were then taken every hour or every two hours, for from six to ten hours. In the observations in which repeated doses were given, each of these was given immediately after a tracing had been recorded. Generally, an interval of at least two days was allowed to elapse between periods of study in the same patient in order to eliminate the possibility of persistent drug action.

The effects of the following were studied on each patient: (1) a single dose of 0.4 Gm.; (2) a single dose of 0.8 Gm.; (3) repeated doses of 0.4 Gm., given at intervals of two hours, for three doses to five patients and for four doses to one patient.

RESULTS

The results observed are pictured in Fig. 1 and Table I. Figs. 2 and 3 are typical tracings obtained, respectively, in a case of auricular fibrillation (Case 1) and in the case of auricular flutter (Case 6).

In each of the five patients with auricular fibrillation (Cases 1,2,3,4 and 5), the control rate of the circus movement was quite constant from day to day, at least over a period of a few days, but varied widely in different patients. The control rate of the circus movement also remained quite constant in the patient with auricular flutter (Case 6).

Following a single dose of 0.4 Gm., the maximal fall in rate occurred two to four hours after ingestion of the drug. The maximum of slowing in the cases of auricular fibrillation varied in different patients and ranged from 12 per cent of the control rate (Case 3) to 24 per cent (Case 4). In the patient with auricular flutter (Case 6), the fall amounted to only 4 per cent. The effect of the drug wore off gradually. In Cases 1 and 5, there was still a marked slowing ten hours after the dose was taken. In Cases 2, 3, 4, and 6, the effect had disappeared completely or almost completely after eight to ten hours.

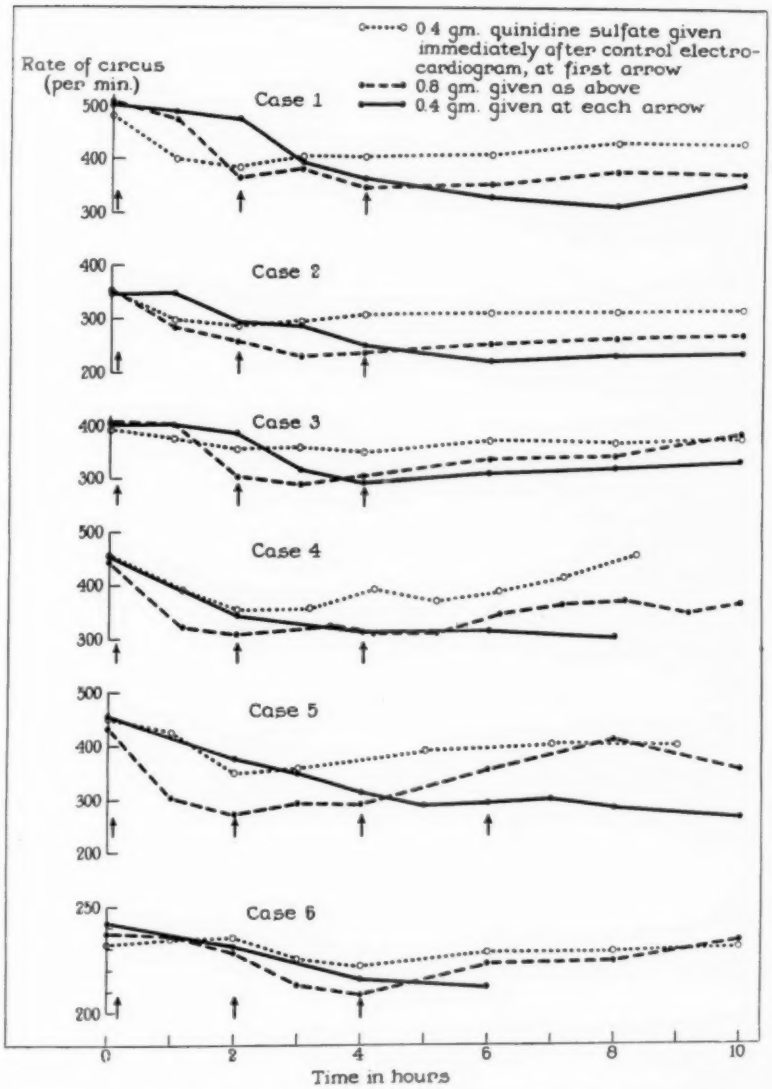

Fig. 1.—Effect of quinidine sulfate on the rate of circus movement in auricular fibrillation and flutter.

Case 1. Rheumatic heart disease, mitral stenosis, auricular fibrillation. Initially fully digitalized and continued on a maintenance dose. First day, 0.4 Gm. quinidine. Two days later, 0.8 gram. Three days later, 0.4 Gm. every two hours for three doses.

Case 2. Coronary heart disease, auricular fibrillation. Initially fully digitalized and maintained on daily ration. First day, 0.4 Gm. quinidine. Two days later, 0.8 gram. Two days later, 0.4 Gm. every two hours for three doses.

Case 3. Coronary heart disease, auricular fibrillation. Initially fully digitalized and maintained on daily ration. First day, 0.4 Gm. quinidine. Two days later, 0.8 gram. Two days later, 0.4 Gm. every two hours for three doses.

Case 4. Rheumatic heart disease, mitral stenosis, auricular fibrillation. Initially fully digitalized and maintained on daily ration. First day, 0.4 Gm. quinidine. Next day, 0.8 gram. Following day, 0.4 Gm. every two hours for three doses.

Case 5. Rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation. Initially fully digitalized and maintained on daily ration. First day, 0.4 Gm. quinidine. Next day, 0.8 gram. Two days later, 0.4 Gm. every two hours for four doses.

Case 6. Auricular flutter, etiology unknown; no organic heart disease. No digitalis. First day, 0.4 Gm. quinidine every two hours for three doses. Two days later, 0.4 gram. Two day later, 0.8 gram.

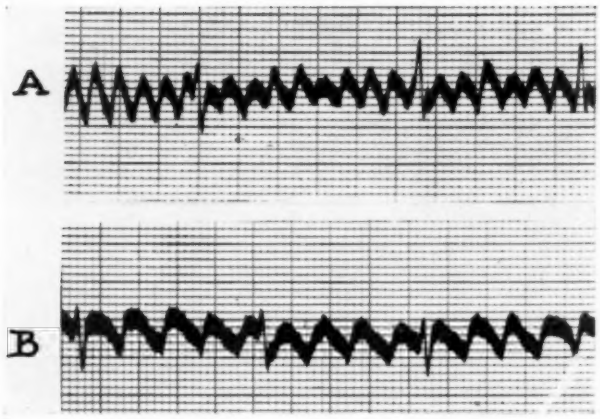

Fig. 2.—Chest lead of Case 1: Patient received 0.4 Gm. quinidine at 9:10 A.M., 11:05 A.M., and 1:00 P.M. *A*, Control record, taken at 9:05 A.M.; circus rate, 500 per minute. *B*, Record taken at 5:00 P.M.; circus rate, 315 per minute.

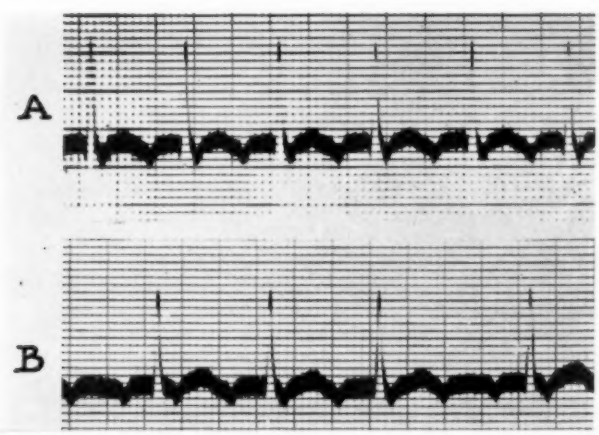

Fig. 3.—Lead II of Case 6. Patient received 0.4 Gm. quinidine at 9:30 A.M., 11:30 A.M., and 1:30 P.M. *A*, Control record, taken at 9:25 A.M.; circus rate, 244 per minute. *B*, Record taken at 3:30 P.M.; circus rate, 212 per minute.

TABLE I. MAXIMAL SLOWING OF THE CIRCUS RATE PRODUCED BY VARIOUS DOSAGES OF QUINIDINE IN PATIENTS WITH AURICULAR FIBRILLATION AND FLUTTER

CASE NO.	RHYTHM	SLOWING AFTER QUINIDINE, IN PER CENT OF THE CONTROL RATE		
		0.4 GM.	0.8 GM.	0.4 GM. EVERY TWO HOURS
1	Fibrillation	20	31	37*
2	Fibrillation	18	35	37*
3	Fibrillation	12	29	27*
4	Fibrillation	24	31	34*
5	Fibrillation	22	37	41†
6	Flutter	4	10	12*

*Received three doses.
†Received four doses.

Following a single dose of 0.8 Gm., the maximal effect also was obtained from two to four hours after ingestion of the drug. In the cases of auricular fibrillation, the maximum of slowing varied in different patients and ranged from 29 per cent of the control rate (Case 3) to 37 per cent (Case 5). In every instance, the fall in the circus rate was greater after 0.8 Gm. than after 0.4 gram. As seen in Table I, the ratio between the size of the dose and the percentage of slowing was maintained in two cases only (Cases 2 and 3). An effect of almost maximal intensity sometimes persisted for several hours (Case 4), after which the action of the drug slowly and progressively decreased. However, ten hours after ingestion of the drug, a marked slowing of the circus rate persisted in most of the cases of auricular fibrillation (Cases 1, 2, 4, and 5). In the case of auricular flutter (Case 6), the slowing with 0.4 Gm. was slight (4 per cent) and much more marked (10 per cent) with 0.8 gram. The ratio between the size of the dose and the percentage of slowing was also maintained in this case. The effect of quinidine was much less marked in auricular flutter than in auricular fibrillation.

When three or four doses of 0.4 Gm. each were given at intervals of two hours, the slope of the curve of slowing of the circus rate varied, depending upon the rapidity with which any given dose produced its full effect. As has been pointed out in the observations made on the effect of single doses, this was not the same in each case. The maximum of slowing was considerably greater than that caused by a single dose of 0.4 Gm. but was very little more marked than that produced by a single dose of 0.8 gram. The maximal effect occurred much later with the repeated doses than with the single dose. Again, slowing was less marked in auricular flutter than in fibrillation.

SUMMARY AND CONCLUSION

1. In six patients, five with auricular fibrillation and one with auricular flutter, a study was made of the effect of varying dosages of quinidine sulfate on the rate of the circus movement. Each patient received on different days a single

dose of 0.4 Gm., a single dose of 0.8 Gm., and repeated doses of 0.4 Gm. every two hours for three or four doses.

2. The control rate of the circus movement varied greatly in different patients with auricular fibrillation but remained quite constant in the same patient during the relatively short periods of observation covered by this study.

3. The maximal effect of a single dose of quinidine (0.4 or 0.8 Gm.) was observed two to four hours after the drug was taken. The extent of the fall in circus rate varied in different patients and was not always proportional to the size of the dose. In one case of auricular flutter, slowing was relatively slight compared with that noted in five cases of auricular fibrillation.

4. In two cases after doses of 0.4 Gm., and in four cases after doses of 0.8 Gm., a marked slowing in the rate of the circus movement persisted for as long as ten hours.

5. After doses of 0.4 Gm. were given every two hours for three or four doses, in most cases the maximal effect was only slightly greater than that observed after a single dose of 0.8 Gm.; but the peak of the effect occurred later, usually two to four hours after the last dose. The therapeutic implication of this observation is obvious, especially in cases in which rapid results are desired.

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EXPERIENCES WITH A NEW SYNTHETIC ANALGESIC, AMIDONE*: ITS ACTION ON ISCHEMIC PAINS OF OCCLUSIVE ARTERIAL DISEASES

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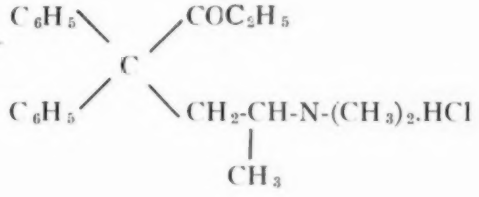
PAIN due to persistent ischemia in occlusive arterial diseases is usually severe and prolonged. The anxiety, restlessness, loss of sleep, and general deterioration of pain resistance not only undermine the general strength of the body but also increase the vasoconstriction in the peripheral arterial circulation. As a result, vasodilatation and development of collateral circulation, which are important aims of treatment, are seriously interfered with and the ischemic, gangrenous process tends to spread. The persistence of pain frequently forces the patient or the physician to seek surgical intervention before a sufficient collateral circulation has been established or a line of demarcation attained.

Narcotic analgesia has not been too satisfactory. The results of surgical procedures such as peripheral nerve section, crushing, alcohol injection, sympathectomy, and arteriectomy have been disappointing. Recent methods, including intravenous ether in saline, intravenous alcohol, and the histidine-ascorbic acid treatment, have likewise been found lacking in the satisfactory control of pain. In the evaluation of any new analgesic, enthusiasm must be guarded.

A new synthetic drug known as Amidone† (chemically, 6-dimethylamino-4, 4-diphenyl-3-heptanone hydrochloride) gives promise of being of value in controlling ischemic pain in peripheral vascular disease. It has the following structural formula:



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†Now known as Methadon (Methadon, generic term for 6-dimethylamino-4, 4-diphenyl-3-heptanone). Report of the Council on Pharmacy and Chemistry, J. A. M. A. 134: 1483 (Aug. 23), 1947.
Now covered by the Harrison Narcotic Act (July 31, 1947).

TABLE I. CLINICAL FINDINGS AND RESULTS OF AMIDONE IN EIGHTEEN PATIENTS WITH OCCLUSIVE ARTERIAL DISEASE*

NO.	AGE AND SEX	DIAGNOSIS	SYMPTOMS	PREVIOUS MEDICATION	RESULTS WITH AMIDONE	REACTIONS
1	60 M D. S.	Arteriosclerosis obliterans (diabetes) with recent midthigh amputation	Phantom limb pain and severe nocturnal cramps	Barbiturates, salicylates, codeine, and morphine	Considerable relief. Sleeps 6-8 hours	Lightheaded and nauseated when ambulatory
2	59 F H. M.	Arteriosclerosis obliterans (diabetes) with gangrene of toes and foot (left)	Rest pains, severe and constant	Morphine every 4 hours with partial relief	Complete relief. Has had over 2400 mg.	None
3	42 M J. J.	Arteriosclerosis obliterans. Marked calcification of aorta and iliacs	Severe paresthesias on walking a few steps	Barbiturates, codeine, and salicylates	Paresthesias relieved	Lightheaded on 5 mg. with no relief. Relief with 10 mg. but lightheadedness too severe
4	61 M E. T.	Arteriosclerosis obliterans (diabetes)	Severe paresthesias and nocturnal pains	Salicylates, codeine, and morphine	Complete relief at night. Partial relief during day. Has had over 1000 mg.	Slight nausea during day, occasional
5	53 M S. D.	Thromboangiitis obliterans, severe, all extremities	Severe pain in ulcerated and infected fingers	Morphine every four hours with partial relief	No relief (oral or intramuscular)	Diarrhea and urinary frequency on oral. Urinary frequency parenterally
6	66 F T. S.	Arteriosclerosis obliterans (diabetes)	Nocturnal cramps, severe	Barbiturates, codeine, quinine	Complete relief	None
7	71 M S. L.	Arteriosclerosis obliterans (diabetes) with gangrene, foot	Rest pain, severe	Morphine and Dilaudid	Complete relief	Lightheaded and nauseated when erect
8	71 M M. G.	Arteriosclerosis obliterans. Bronchial asthma	Nocturnal cramps, severe	Barbiturates, codeine, quinine	Complete relief	Slight nausea on sitting or standing. Coughing hindered
9	72 M S. A.	Arteriosclerosis obliterans	Nocturnal cramps, severe	Barbiturates, codeine, quinine	Complete relief	Severe nausea and lightheadedness on standing

10	78 M H. B.	Arteriosclerosis obliterans	Nocturnal cramps	Barbiturates, quinine	Partial relief	None
11	49 M H. M.	Arterial occlusion, embolic, distal end of aorta. Etiology unknown	Rest pain, severe. Nocturnal cramps, severe	Barbiturates, salicylates, codeine, and morphine	Complete relief	None
12	59 F J. S.	Arteriosclerosis obliterans	Nocturnal cramps, severe	Salicylates, quinine, codeine	Complete relief	None
13	59 M A. K.	Arteriosclerosis obliterans	Nocturnal cramps, severe	Quinine, codeine	Complete relief	None
14	48 F L. F.	Arterial occlusion, embolic, distal end of aorta. Rheumatic heart disease and bronchial asthma	Rest pain, severe	Morphine and Dilaudid	Complete relief	Hemorrhagic urticaria. Coughing hindered
15	59 M S. R.	Arteriosclerosis obliterans (diabetes) with recent midthigh amputation	Stump pain, nocturnal cramps	Morphine, Demerol, codeine	Partial relief	None
16	74 M E. R.	Arteriosclerosis obliterans	Rest pains	Salicylates, codeine	Complete relief	Short periods of confusion, slight nausea even when recumbent
17	75 M S. L.	Arteriosclerosis obliterans	Rest pains	Morphine, salicylates, codeine	Partial to complete relief	Nausea even while recumbent. This disappeared on continued administration
18	60 F T. W.	Arteriosclerosis obliterans	Nocturnal cramps	Quinine, salicylates, codeine	Complete relief	Lightheadedness and nausea on ambulation the morning following one evening dose of 5 mg.

***Amidone was administered to two additional patients, one with chronic bilateral thrombophlebitis of the deep veins of the calves and one with scleroderma. In both patients, Amidone resulted in complete relief of severe pain.**

All patients with occlusive arterial disease suffered from intermittent claudication. A few suffered from pains on dependency or weight bearing. These were unaffected by Amidone.

This drug was first produced in Germany in 1941, where it was known as 10,820. Its pharmacology and preliminary clinical investigations have been reported by Scott and associates,[1] Scott and Chen,[2] and others.[3-6]

Amidone was given to a series of eighteen patients suffering from occlusive arterial diseases associated with marked ischemic pain. All of these patients suffered from one or more of the following symptoms: rest pain, nocturnal cramps, intermittent claudication, paresthesias, ulceration, and gangrene. All had been observed for considerable periods of time. Extensive therapeutic procedures had been instituted at one time or another. These included intermittent venous occlusion, reflex heat, ionization with histamine or mecholyl, histidine and ascorbic acid, intravenous ether and saline, intravenous alcohol, oral medication such as aminophylline or other xanthine derivatives, potassium iodide, barbiturates, salicylates, and codeine. Morphine, Dilaudid, and Demerol had also been used. Most of these patients were hospitalized.

Amidone was administered orally in 5 to 15 mg. capsules or tablets, using dextrose as a filler. Five milligrams in each cubic centimeter of distilled water were used for intramuscular administration. Placebos were given in one case only, as these patients had received considerable medication, especially narcotics, prior to Amidone therapy. The data are summarized in Table I.

RESULTS AND DISCUSSION

Relief of pain was usually prompt and satisfactory. Pharmacologic activity was apparent within forty minutes after receiving Amidone orally or parenterally. Relief lasted as long as sixteen hours. Rest pains, pains of ulceration and gangrene, paresthesias, and nocturnal cramps were relieved. Intermittent claudication and pains of dependency and weight bearing were unaffected. A sedative action was apparent at night. Patients slept soundly and awoke refreshed. There was no euphoria. Patients stated that they knew pains were present but they seemed to belong to someone else. One patient stated that his leg which previously had given him considerable pain felt detached from his body. He felt as if he had no leg. Prior to Amidone therapy, considerable narcotic analgesia was necessary in this case.

There was no addiction or increase in tolerance necessitating increase in dosage. As the pain subsided, administration became less frequent and in a few cases it was discontinued completely. One patient received over 2,400 mg. within a period of two months. A midthigh amputation became necessary. Following surgery, the pain was relieved, and the Amidone was discontinued. The patient asked for it, stating that she missed it. Twenty-four hours after the drug had been stopped the patient had completely forgotten about it. Another patient received over 1,000 milligrams. He discontinued Amidone for days at a time. As the pain returned, Amidone therapy again became necessary. For very severe pain, 15 mg. would not suffice and 30 mg. would be necessary. The increase in dosage was only transient. Placebos were given in this case but had no effect upon the pain.

The pain relief was not due to any increase in peripheral arterial circulation. Blood pressure, respiration, heart rate, oral temperature, skin temperature, skin color, oscillometric determinations, urine, blood count, and prothrombin time were unaffected. Constipation was a rare complaint. Urinary difficulties were not present except in Case 5, where frequency followed oral or parenteral administration. Pupillary changes were not noted.

Unpleasant side reactions were few when patients were recumbent. Reactions in the erect positions were frequent, except in two cases. The administration of Amidone in the ambulatory patient usually produced uncomfortable reactions which precluded its use entirely except in the occasional cases where reactions were completely absent. These side reactions were lightheadedness, nausea, and vomiting. These reactions appeared upon sitting, standing, or walking and were relieved upon lying down. The lightheadedness was not vertigo or dizziness. It was present with the eyes opened or closed. There was no nystagmus. Patients stated that they felt that they would fall over if gently pushed. In two cases, ingestion of 5.0 mg. of Amidone at bedtime gave complete relief of pain. However, upon arising, lightheadedness and nausea appeared and persisted until the forenoon. The duration of the effect in each case was sixteen hours. Patient 12 stated that she would rather be lightheaded and nauseated than suffer from painful, sleepless nights. The nausea and vomiting were unaffected by carminatives or barbiturates in most cases. Severity and persistence of these symptoms usually varied directly with the size of the dose, although 5.0 mg. were sufficient to bring on severe symptoms in a few cases. In occasional cases, nausea was present and even marked in the recumbent position. Usually, the more nausea, the less effective was the analgesia. It was occasionally noted that as the pain decreased, the nausea increased until the dosage was reduced or discontinued.

The lightheadedness on assuming the erect position was not accompanied by change in blood pressure or heart rate. These varied very little. Decrease of lightheadedness and nausea did occur occasionally on persistence of administration of Amidone. It was found that ingestion of Amidone with meals was more likely to bring on nausea than administration between meals. One patient obtained such dramatic relief of her nocturnal cramps that she tried Amidone during the day while ambulatory. Nausea and vomiting were so marked that she thought she was pregnant.

Two patients, Cases 8 and 14, also suffered from bronchial asthma at the time of the administration of Amidone. Although the asthma was not aggravated, these patients complained of difficulty in expectoration. There appeared to be an inhibition of the cough reflex. This could be explained as a codeine-like action.

A hemorrhagic urticaria appeared in one patient (Case 14) after receiving 925 mg. of Amidone over a period of seventeen days. This patient had a long history of allergic reactions including a marked skin sensitivity to a multitude of substances. Amidone therapy had no detrimental effect on her asthma which was acute during the entire period. On the evening of the seventeenth day, this

patient developed a generalized urticaria which rapidly became edematous and very extensive. The face was markedly edematous. The urticaria was particularly severe about the rectum and genitalia. All medication was discontinued. Within twenty-four hours the lesions became hemorrhagic. Itching and discomfort became severe. The oral temperature rose to 101.6°F. and remained until the rash subsided. Adrenalin and Pyribenzamine were administered frequently. The acute phase subsided within seventy-two hours and all signs were completely absent within two weeks. In addition to Amidone, this patient had been receiving aminophylline, saturated solution of potassium iodide, phenobarbital, codeine, Cedilanid, and Dicumarol. The Dicumarol had been given up to the day the rash appeared. The prothrombin time had reached 29 seconds, against a normal of 19 seconds. After the subsidence of the rash, Dicumarol and Cedilanid were resumed. The ischemic pain became minimal and was adequately controlled with codeine.

During the height of the eruption the platelets numbered 679,420. The blood count, culture, red blood cell fragility, and coagulation time (Dukes and slide method) were normal. The stools on one occasion showed 2 plus occult blood. A blood count, taken eight days after the onset of the eruption and after it had subsided, revealed 39,800 white blood cells, with 93.5 per cent polymorphonuclear leucocytes. The platelet count was normal. Previously, this patient had tolerated all medication well. Whether the eruption was due to Amidone, or the combination of Amidone and Dicumarol, or to other drugs is difficult to determine. Since it cleared up rapidly on discontinuance of the Amidone, it is possible that this substance was the causative agent.

SUMMARY AND CONCLUSIONS

1. Amidone appears to act upon the central nervous system. Its action resembles morphine. In the series of patients studied there was no addiction or increased tolerance.

2. Amidone was well tolerated by the majority of cases when the patient was in the recumbent position. Sitting, standing, or walking brought on lightheadedness, nausea, or vomiting in a large percentage of cases. These symptoms were severe enough to prevent further use of the drug in some patients. Occasionally, patients could not tolerate Amidone even in the recumbent position. In these patients, the analgesic effect was minimal.

3. Administered orally in 5 to 15 mg. doses, Amidone satisfactorily controlled ischemic rest pain, paresthesias, and nocturnal cramps of occlusive arterial diseases and effectively replaced narcotic analgesics.

4. It was ineffective in alleviating intermittent claudication and pain brought on by dependency or weight bearing.

5. A hemorrhagic urticaria developed during the administration of Amidone in one case.

6. There was no effect on blood pressure, heart rate, respiration, surface temperature, or oscillometer readings. The relief of pain was not due to any

increase in peripheral arterial circulation, or to action on the peripheral nerves or autonomic nervous system.

7. The occurrence of lightheadedness, nausea, and vomiting in ambulatory patients who are receiving Amidone appears to be a safeguard in the control of patients suffering from ischemic lesions in peripheral vascular diseases in which bed rest is a very important factor in therapy.

ADDENDUM

Since this report was submitted, ten additional cases of occlusive arterial diseases with ischemic pain have been given Amidone orally. Morphine had been given to several previously. These cases included gangrene of the toes due to arteriosclerosis obliterans (one case); ulceration of the finger tips due to Raynaud's disease (one case); and nocturnal cramps, rest pains, and severe paresthesias, such as persistent burning, due to arteriosclerosis obliterans (eight cases). Nausea and vomiting were present upon ambulation in two cases. Facial edema occurred in one case. Good to excellent results were obtained in nine patients who could tolerate Amidone. Seven of these nine patients tolerated Amidone when ambulatory as well as in recumbency; two patients tolerated the drug only in recumbency. Amidone was ineffective in the one case in which facial edema occurred. There was no evidence of addiction in any case. Pain cycles seemed to be effectively broken.

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ELECTROCARDIOGRAPHIC CHANGES IN PULMONARY COLLAPSE THERAPY. I

Artificial Pneumothorax

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IN PRACTICALLY any group of patients, individuals are commonly seen whose history, symptoms, or clinical findings suggest the necessity of an electrocardiogram as an aid in diagnosis. Certainly we have found this to be true among tuberculous patients in a sanatorium. In such an institution many of these individuals will have been subjected to collapse therapy, and in these persons it may be difficult to determine which of the electrocardiographic changes seen are due to myocardial involvement and which are due to collapse therapy. In an attempt to clarify this problem, we have made an electrocardiographic study of a group of patients undergoing collapse therapy. This report deals with our findings in artificial pneumothorax.

METHOD

Electrocardiographic tracings were taken in a consecutive series of patients, the criterion for whose selection was solely the fact that they had been passed by the hospital staff for therapeutic pneumothorax. Electrocardiograms and chest x-ray films were made prior to the institution of the pneumothorax and soon after the pneumothorax was established. In each case, the x-ray and electrocardiogram following the pneumothorax were made on the same day or, in a few cases, one day apart, and before another pneumothorax refill had been given. The purpose of this was to demonstrate as accurately as possible the degree of pulmonary collapse at the time of the electrocardiogram. The electrocardiograms were made at a variable time after the preceding pneumothorax refill, ranging from the day of the refill to five days later.

All electrocardiograms were made with the patients in the supine position. To minimize individual variability in placement of electrodes, all tracings were taken by one or the other of the authors. In addition to the three conventional limb leads, chest Leads CF_1, CF_2, CF_4, and CF_5 were taken; CF_1 because we felt it might be informative where there were shifts of the heart, and the others because they represent a combination of chest leads which have been found to be of high diagnostic value.[1,2] Each record was interpreted as to its normality or abnormality, and the degree and variety of the latter. In addition, measure-

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ments were made of the rate, P-R interval, QRS duration, the direction and amplitude of the various complexes in each lead, and the numerical value of the electrical axis of the QRS complex, as measured on the triaxial reference system.

The chest plates were posteroanterior views made at a target-film distance of five feet (the routine technique used at the Robert Koch Hospital). Lateral displacement of the heart was determined by measuring the lateral shift of the left contour of the heart shadow at the level of the superior border of the tenth rib, posteriorly. This point on the cardiac silhouette falls on the left ventricular contour. The horizontal distance (in inches) between this point and the inner bony margin of the left chest wall before and after pneumothorax is shown in Table I.

RESULTS

A total of twenty-three consecutive cases was analyzed, ten with right pneumothorax and thirteen with left pneumothorax. The significant findings are listed in Table I and summarized in Table II. Electrocardiograms of representative cases are shown in Fig. 1.

P-Wave.—P-wave changes have previously been reported in pneumothorax. Fox and Kremer[3] found inversion of P_1 and Anderson[4] noted a tendency toward diminution of P_1 in right pneumothorax. Burton and Mehlman[5] reported a very large, deeply inverted P wave in Lead CF_2 in a case of spontaneous right pneumothorax. In our series, the P-wave changes were slight and not consistent in left pneumothorax. In right pneumothorax, there was a tendency toward slight decrease in amplitude of P_1 and increase in amplitude of P_3.

P-R Interval.—This was within the normal range of 0.10 to 0.21 sec.[1] in each case, and showed no, or minimal, change following pneumothorax.

QRS Changes in the Limb Leads.—Frequent presence of S_1[6] and low voltage of QRS in certain leads[6,7] have been described in pneumothorax. These findings are not abnormal, per se, by modern standards. No abnormalities of either the form or duration of the QRS attributable to pneumothorax were found. A tendency toward some decrease in amplitude of QRS_1 was seen fairly consistently in right pneumothorax.

Changes in the Electrical Axis of the QRS.—A number of earlier papers on the electrocardiogram in pneumothorax deal with shifts in the electrical axis of the QRS brought about by pneumothorax. Bronfin and associates[8] in 1929 found a shift in the electrical axis to the right in twenty-one of forty-five cases of pneumothorax, and felt that this was more common in cases that improved under therapy. Anderson[4] in 1929 found an abnormal degree of right axis deviation (90° or more) in nine of twenty-five right and in three of twenty-five left pneumothoraces. Treiger and Lundy[7] in 1934 found in uncomplicated pneumothorax that eight of nine cases of left pneumothorax showed a shift in the electrical axis to the right, the remaining case showing no shift; all of eleven cases of right pneumothorax showed a shift of the axis to the right. The amount of

TABLE I. ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY PNEUMOTHORAX IN EACH CASE

PATIENT	SEX AND AGE	TB DIAG.*	PNEUMO SIDE	AGE OF PNEUMO (DAYS)	HEART POSITION†	QRS AXIS†	CHANGES IN LIMB LEADS I AND III		CHANGES IN PRECORDIAL LEADS				REMARKS
							T WAVE LARGER	T WAVE SMALLER	QRS SMALLER	QRS MORE INVERT.	T WAVE SMALLER	T WAVE INVERT.	
A (S. K.)	F 25	F. A. IV	L	0	2 1/8	+ 35	III		CF_2 CF_4 CF_5	CF_2 CF_4 CF_5	CF_4	CF_2 CF_5	T_3 larger than T_1; atalectasis of left lower lobe
				5	3 1/8	+ 38							
B (L. R.)	M 24	F. A. III	L	0	2 3/8	+ 35		I	CF_1 CF_2 CF_4 CF_5			CF_2 CF_4 CF_5	T_3 larger than T_1
				23	3	− 32							
C (A. F.)	F 29	M. A. III	L	0	3 1/8	+ 38		I	CF_1 CF_2 CF_4 CF_5	CF_1 CF_2 CF_4 CF_5	CF_5	CF_2 CF_4	Heart retracted to right before pneumo; almost completely in right chest after pneumo
				19	3 7/8	+ 72							
D (P. D.)	F 15	M. A. II	L	0	2 7/8	+ 82	III	I	CF_2 CF_4 CF_5	CF_1 CF_2 CF_4 CF_5		CF_2 CF_4 CF_5	T_3 larger than T_1
				13	3 1/2	+ 72							
E (G. M.)	M 21	M. A. I	L	0	2 1/2	+ 82	III	I	CF_4 CF_5	CF_2 CF_4 CF_5	CF_4 CF_5		T_3 larger than T_1
				12	3 5/8	+ 77							
F (G. H.)	M 19	M. A. III	L	0	2 7/8	− 20	III	I	CF_2 CF_4 CF_5	CF_1 CF_4 CF_5	CF_2 CF_4	CF_5	T_3 larger than T_1
				12	4 5/8	+ 60							
G (L. I.)	F 58	M. A. II	L	0	2 3/8	+ 70	III	I	CF_2 CF_4 CF_5	CF_4	CF_2 CF_4 CF_5	CF_1	T_3 larger than T_1
				11	3 1/4	+ 79							

H (C. R.)	F 39	F. A. IV	L	0	3/4	+ 85	III	I	CF_2 CF_5	CF_4 CF_5	CF_2 CF_4	CF_5	T_3 larger than T_1; heart retracted to left before pneumo
				6	1 3/4	+ 70							
I (E. C.)	M 29	F. A. II	L	0	2 1/2	+ 53	III	I	CF_4 CF_5	CF_2 CF_4 CF_5		CF_2 CF_4 CF_5	T_3 larger than T_1
				5	4	+ 82							
J (E. B.)	M 40	F. A. II	L	0	2 3/4	+ 73	III	I	CF_2 CF_4 CF_5	CF_4 CF_5		CF_4 CF_5	T_3 larger than T_1; T in CF_2 inverted before pneumo. Broad apical adhesion. Pneumo discontinued
				5	4	+ 68							
K (P. A.)	F 50	F. A. III	L	0	2 1/4	+ 63		I III	CF_4 CF_5	CF_2 CF_4 CF_5		CF_2 CF_4 CF_5	T_3 larger than T_1; pneumo discontinued
				53	3 1/4	+ 61							
L (E. B.)	M 29	F. A. II	L	0	3 5/8	+ 75	III	I	CF_2 CF_4 CF_5	CF_2 CF_4 CF_5		CF_2 CF_4 CF_5	T_3 larger than T_1; pneumo discontinued
				12	4 1/8	+ 77							
M (F. R.)	F 31	F. A. II	L	0	2	+ 38	III		CF_4 CF_5	CF_4 CF_5	CF_4 CF_5		Pneumo discontinued
				19	3 3/8	+ 73							
N (M. B.)	F 23	F. A. II	R	0	1 1/4	+ 62			CF_1	CF_4 CF_5	CF_4	CF_2	Base of heart shifted more than apex
				4	1 1/16	+ 79							
O (S. F.)	F 15	F. A. II	R	0	2 5/8	+ 68	III	I	CF_1	CF_1 CF_5	CF_5	CF_4	T inverted in CF_2 before pneumo; dorsal scoliosis to right, pronounced
				22	2 1/4	+ 77							
P (H. D.)	M 25	M. A. III	R	0	2 5/8	− 35	III	I		CF_2 CF_4			T_3 larger than T_1; control ECG abnormal
				21	2 3/8	− 60							
Q (J. H.)	M 25	F. A. IV	R	0	2 3/4	+ 55	III					CF_2	T_3 larger than T_1; upper lobe adherent
				7	2 3/8	+ 57							

TABLE I. ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY PNEUMOTHORAX IN EACH CASE—(CONT'D)

PATIENT	SEX AND AGE	TB DIAG.*	PNEUMO SIDE	AGE OF PNEUMO (DAYS)	HEART POSITION†	QRS AXIS†	CHANGES IN LIMB LEADS I AND III		CHANGES IN PRECORDIAL LEADS				REMARKS
							T WAVE LARGER	T WAVE SMALLER	QRS SMALLER	QRS MORE INVERT.	T WAVE SMALLER	T WAVE INVERT.	
R (L. I.)	F 58	M. A. II	R	0	2 3/8	+ 70		I III	CF_1	CF_1			
				20	2 5/8	+ 82							
S (C. M.)	F 41	F. A. II	R	0	2 5/8	+ 20		I	CF_1 CF_2 CF_4 CF_5	CF_4	CF_2 CF_4 CF_5		Control ECG abnormal
				13	2 5/8	+ 10							
T (V. W.)	F 34	F. A. II	R	0	2 5/8	+ 37	III	I	CF_1 CF_5		CF_5		Upper lobe diffusely adherent
				5	2 3/8	+ 45							
U (T. J.)	F 24	F. A. III	R	0	1 1/4	+ 79		I	CF_5				Control ECG abnormal, with T-wave inversion in all precordial leads
				30	1	+ 88							
V (H. B.)	M 21	F. A. III	R	0	3 3/8	+ 67		I III					Has pneumoperitoneum also
				9	3 3/8	+ 73							
W (R. D.)	F 18	M. A. III	R	0	2 1/2	+ 35		I III			CF_4 CF_5	CF_2	
				17	2 1/4	+ 48							

*The tuberculosis diagnosis follows the criteria given in "Diagnostic Standards and Classification of Tuberculosis," published by the National Tuberculosis Association, New York, 1940 edition; *MA* and *FA* denoting moderately advanced and far-advanced disease, respectively, and the numerals II, III, and IV denoting slight, moderate, and severe symptoms, respectively.

†Procedure for measurement of heart position and QRS axis are explained in the text.

TABLE II. SUMMARY OF ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY PNEUMOTHORAX

	LEFT PNEUMOTHORAX	RIGHT PNEUMOTHORAX
Total cases	13	10
Cases showing a shift of axis of:		
+ 1° to +15°	3	7
Over +15°	4	1
− 1° to − 15°	5	1
Over − 15°	1	1
Cases showing in limb leads:		
T_1 smaller	11	8
T_3 larger	10	4
T_3 larger than T_1	11	2
All three changes	8	1
Cases showing in precordial leads (except CF_1):		
QRS smaller in one or two leads	5	2
QRS smaller in all three leads	8	1
QRS more inverted in one or two leads	5	4
QRS more inverted in all three leads	7	0
T smaller in one or two leads	6	4
T smaller in all three leads	1	1
T inverted in one or two leads	5	4
T inverted in all three leads	5	0
T smaller or inverted in all three leads	10	1

shift was variable, and was greater in left (average 27°) than in right (average 14.5°) pneumothorax. Fluid in either pleural cavity or adhesions near the cardiac apex tended in their series to cause a shift of the electrical axis of the QRS to the left.

Our series showed some tendency toward a shift of the axis to the right. This was more noticeable in right pneumothorax than in left. In eight of ten cases of right pneumothorax, there was a shift of the electrical axis to the right; in only one case did this shift amount to over 15° (Case N, with change of 17°). Two cases showed a shift of the axis to the left (Cases P and S). In neither of these was the control electrocardiogram normal. In our thirteen cases of left pneumothorax, seven showed an axis shift to the right; in four of these the shift amounted to more than 15°. Six cases showed a shift of the axis to the left, this being more than 15° in only one case. We found no definite correlation of the direction or degree of axis shift with either the amount or the effectiveness of the pneumothorax, with the presence of adhesions, or with the amount of shift of the position of the heart. Our conclusion was that probably the axis shift is correlated at least partly with factors not obvious by our method of study, perhaps with rotation of the heart on its longitudinal or transverse axes.

T-Wave Changes in the Limb Leads.—Previous publications have dealt little with T-wave changes in the limb leads in pneumothorax. Master,[6] in his early paper (1929), noted small T waves three times in seven cases of pneumothorax. Hansen and King,[9] in 1930, found in left pneumothorax some tendency of T_1 to

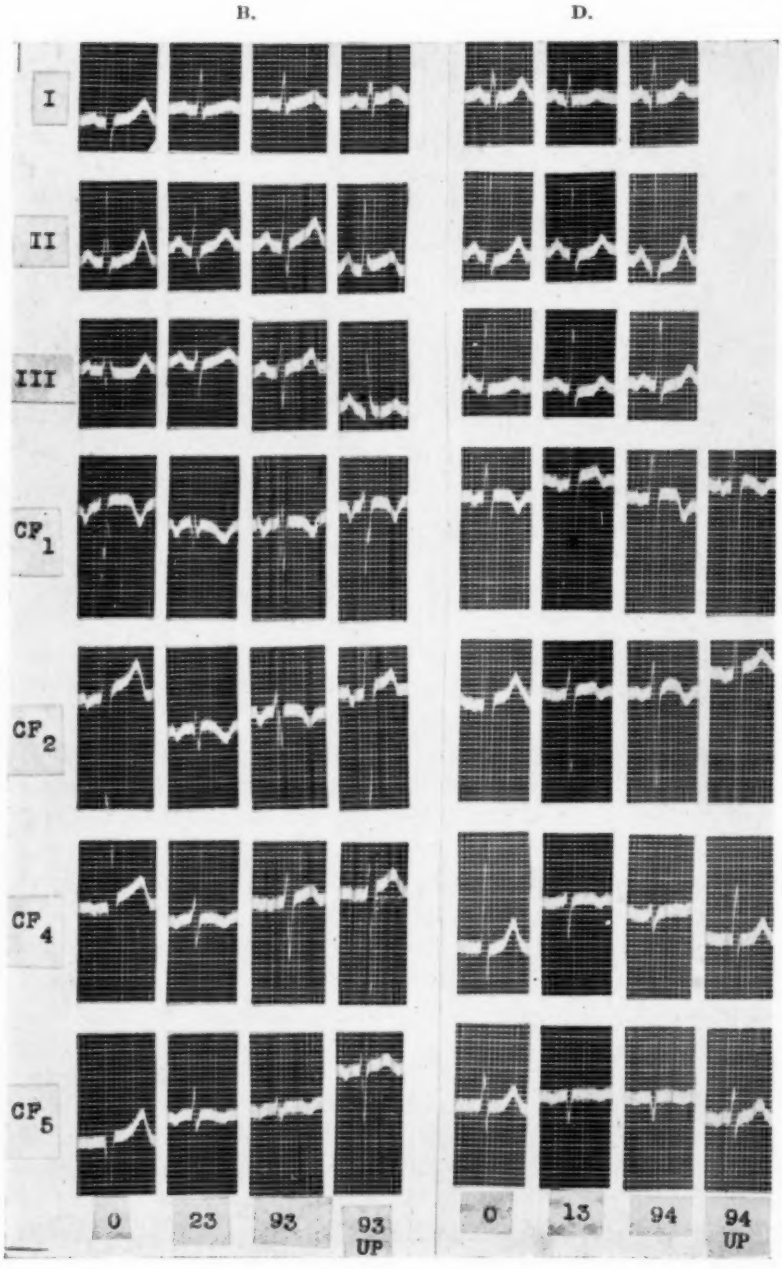

Fig. 1.—Single complexes from each lead in illustrative cases of pneumothorax. The first tracing in each individual case is the precollapse control record. The time after institution of the pneumothorax (in days) when the tracing was taken is indicated below each tracing. Tracings marked *UP* are those made with the subject in a sitting position. The tracing in Case L marked *DIS.* was taken following discontinuation of the pneumothorax and absorption of the air. Cases B, D, E, and L are cases of left pneumothorax, and show in varying degree the changes described in the text, Case D best illustrating the complete pattern and Case E showing the least pronounced changes of all our cases.

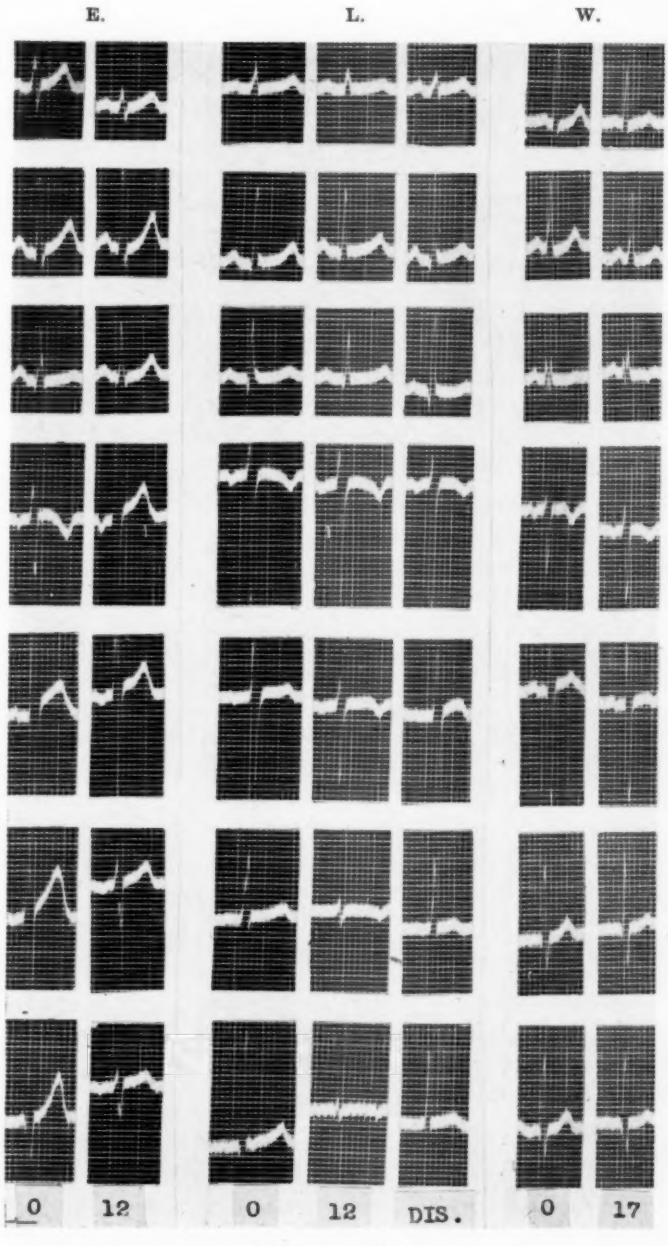

Fig. 1.—Cont'd.

In Cases B and D a repeat tracing about three months after institution of the pneumothorax shows a tendency for the changes ascribed to the pneumothorax to persist, with, however, some alteration, that is, T in CF_4 in Case B. These two cases also illustrate the reversibility of the precordial lead changes with assumption of the sitting position; Case D demonstrates this particularly well. In Case L a tracing taken following discontinuation of the pneumothorax and complete absorption of the air demonstrates the reversibility of the changes with disappearance of the pneumothorax space. Case W is a case of right pneumothorax showing about the average extent of changes following pneumothorax.

decrease or remain unchanged and often T_3 became larger. In right pneumothorax, T_1 tended somewhat to decrease and T_3 showed no consistent change.

In our cases, there was a definite tendency for T_1 to become smaller after pneumothorax, both right (eight of ten cases) and left (eleven of thirteen cases). The T wave of Lead III became larger in ten of our thirteen cases of left pneumothorax. In right pneumothorax, T_3 showed no consistent change. Changes in T_2 showed no consistency. Because of the concomitant increase in the size of T_3 and decrease in the size of T_1 in left pneumothorax, the finding of a T_3 larger than T_1 was present in eleven of our thirteen cases of left pneumothorax.

QRS Changes in the Precordial Leads.—In 1937, Master and associates[10] reported small or absent R waves in a left precordial lead (electrode was placed just inside the apex beat in the fourth or fifth intercostal space) in cases of spontaneous pneumothorax (side not specified). Cases showing diminished or absent R waves in Lead IVF in left pneumothorax were published by Master and associates in 1941[11] and by Littmann[12] in 1946 (the latter reported two cases with spontaneous mediastinal emphysema and left pneumothorax).

In right pneumothorax, we found no important changes in the QRS complexes of the precordial leads. In five of our ten cases, the QRS in Lead CF_1 was smaller than in the precollapse record. Only two cases showed a smaller QRS in more than one precordial lead. Five cases showed a QRS more inverted in one or more precordial leads. In none of these was the inversion enough to be striking or to be considered abnormal.

In left pneumothorax, consistent and significant changes were present in the QRS complexes of the precordial leads. All of our thirteen cases had diminished amplitude of the QRS complex in two or more precordial leads. This tended to be more pronounced in the leads situated farther to the left, and often was very striking. In eleven of the thirteen cases, the QRS was more inverted in two or more chest leads, and in one additional case, in Lead CF_4 only. Again, this inversion was often of a pronounced degree in the precordial leads situated farther to the left.

T-Wave Changes in the Precordial Leads.—In right pneumothorax no consistent precordial T-wave changes were found. In several cases, a decrease in amplitude in one or more leads, and in four cases, T-wave inversion in one lead (Lead CF_2 three times and CF_4 once) were seen.

Cases with left pneumothorax had a definite tendency to T-wave alterations in the precordial leads. Lead CF_1 is excluded in this discussion because the T wave may normally be inverted in this lead. In all of our cases with left pneumothorax the T waves became smaller or inverted in two or more of precordial Leads CF_2, CF_4, and CF_5. In five of the cases the T wave became inverted in all three precordial leads, in three more cases it became inverted in two leads, and in two it became inverted in one lead. Thus, in ten of thirteen cases with left pneumothorax, the T wave became inverted in one or more of Leads CF_2, CF_4, and CF_5. In three cases T waves became smaller in two or three precordial leads without inversion occurring.

Littmann[12] pointed out that the changes in the precordial lead consequent to left pneumothorax were present only in the supine, and not in the erect, position. In three cases, we took electrocardiograms in the sitting position immediately after taking tracings in the usual supine position (in one of these cases only the precordial leads were taken). Each of these cases showed a tendency for the precordial lead changes ascribed to the pneumothorax to disappear (Fig. 1, Case B). Our findings thus support those of Littmann.

Reversibility of Changes.—In four cases of left pneumothorax, we had the opportunity to compare electrocardiograms following discontinuation of pneumothorax. After complete resorption of the air, the tracing became comparable with the precollapse tracing in all cases (Fig. 1, Case L).

Permanence of Changes.—In three of the cases of left pneumothorax, repeat tracings were taken several months after the institution of the pneumothorax. The changes found immediately after the pneumothorax were seen to persist (Fig. 1, Case B). Whether there might be further changes in the course of time is not revealed in this study.

DISCUSSION

Many data have appeared in the recent medical literature concerning electrocardiographic effects of noncardiac conditions. In 1946, Sensenbach[13] was able to compile a list of forty-seven conditions not due to myocardial disease which give rise to electrocardiographic changes. Such information obviously has a beneficial effect on accurate electrocardiographic diagnosis, and further information of this sort should be sought.

It has long been known that pneumothorax will produce electrocardiographic alterations. One of the purposes of this study was to review the available data on this subject and to determine whether the electrocardiographic changes produced by pneumothorax will fit into a pattern of any diagnostic utility.

In right pneumothorax, the changes produced, while noticeable in each case, were too variable or else too unspecific to be useful diagnostically. The more consistent changes were as follows: (1) P_1 often became smaller, and QRS_1 also tended to become smaller; (2) there was usually a shift of the electrical axis of the QRS, more often to the right than to the left, and, in our series, not of great magnitude; (3) the T wave of Lead I tended to decrease in amplitude; and (4) in the precordial leads, the only significant change seen was occasional T-wave inversion in Lead CF_2 or CF_4.

In left pneumothorax, in contrast with right, the changes showed much more consistency, of such degree that in our series they took the character of a specific pattern. The T wave of Lead I usually decreased and T_3 usually increased in amplitude, so that T_3 became larger than T_1. This is the reverse of the usual T_1-T_3 relationship (Dressler[14]), and left pneumothorax should certainly be added to Dressler's list of conditions giving rise to such an altered relationship.

The direction of axis shift in this series was not consistent, being toward the left six times and toward the right seven times. The chest leads were more or less characteristic in twelve of the thirteen cases, the changes being a decrease in amplitude and tendency to inversion of QRS, with the R often becoming abnormally small. This was usually more pronounced in the chest leads farther to the left. The T waves became smaller or inverted in the chest leads. The total pattern was quite characteristic, with a small T_1, a larger T_3, and, in the chest leads, small and inverted QRS complexes, and small or inverted T waves. If further experience bears out the specificity and dependability of this pattern of left pneumothorax, it would assume importance for another reason. Master and associates[11] emphasized the great clinical similarity which may exist between the onset of acute myocardial infarction and of spontaneous left pneumothorax. The acute left-sided chest pain and the dyspnea characteristic of spontaneous pneumothorax on this side may certainly be confused with a myocardial infarction. Moreover, the electrocardiogram with T_1 smaller than T_3, small or absent R waves, and inverted T waves in the chest leads bears some resemblance to an anterior wall infarction pattern. Even though the presence of the pneumothorax is detected clinically, the recognition that this pattern is seen in left pneumothorax might eliminate confusion in such cases, resulting from the suspicion, based on the electrocardiographic findings, of superimposed myocardial involvement.

It is of interest that we were unable to correlate the degree of electrocardiographic alteration, either with the degree of cardiac displacement or with the presence or absence of adhesions. The work of Todd and Anderson[15] is important in this connection. In studying the effect on pneumothorax of changing atmospheric pressures, they found no significant change in the electrocardiogram (including Lead IV) in a case of left pneumothorax in which a change in atmospheric pressure caused the heart to shift two inches from left to right.

In attempting to account for the changes noted, we felt that at least two factors were responsible: (1) an alteration of the electrical field of the heart in relation to the body, brought about by a change in the heart's position with rotation of the heart on its various axes; and (2) interposition of a nonconductor (air) between the heart and the chest wall. The latter factor would be expected to be of more significance in left than in right pneumothorax because of the position of the heart in the left chest and the location of the precordial electrode on the left chest. Both of these factors, changes of the heart's position with relation to the body and interposition of nonconductors between the heart and the chest wall, are capable of causing alterations in electrocardiograms.[16-21] That either one is solely responsible for the changes seen in pneumothorax is unlikely. Thus, the experience of Todd and Anderson with pneumothoraces in a pressure chamber and our own inability to correlate x-ray findings with electrocardiographic changes indicate that more than merely changes in the position of the heart is involved. On the other hand, the changes seen in the electrocardiogram when a patient with left pneumothorax changes from the supine to the upright position indicate that more than merely the presence of the pneumothorax space is involved. The conclusion is that the changes must be attributed to an

unknown combination of the two factors of change in orientation of the electrical field of the heart to the body and a change in electrical conductivity of the chest structures due to the layer of nonconducting air between the lung and chest wall. Adhesions, pleural fluid, and so forth would probably add to the complexity of the problem.

SUMMARY AND CONCLUSIONS

1. Electrocardiograms and chest x-ray films were made in a group of tuberculous patients before and after institution of therapeutic pneumothorax. A total of ten cases of right pneumothorax and thirteen cases of left pneumothorax were studied, and alterations in the electrocardiogram following pneumothorax were noted, as were radiographic changes.

2. P waves showed no consistent changes following left pneumothorax. The P wave in Lead I tended to become smaller and P_3 larger after right pneumothorax. P-R intervals were unaffected by pneumothorax.

3. In the limb leads, QRS_1 tended to decrease in amplitude in right pneumothorax. There was a tendency for a shift of the electrical axis of the QRS to the right in right pneumothorax. In left pneumothorax, approximately equal numbers showed a shift of the axis to the right and to the left. The T wave in Lead I tended to become lower in both right and left pneumothorax. In left pneumothorax, T_3 tended to increase in size.

4. In right pneumothorax no important changes were seen in the QRS complexes of the precordial leads. The T wave occasionally became inverted in CF_2 or CF_4 with right pneumothorax. Pronounced and consistent changes were seen in the precordial leads after left pneumothorax. QRS complexes became smaller and inverted, and T waves became lower or inverted. These changes associated with left pneumothorax persisted over the period of several months which our experience covered, and were reversible with discontinuation of the pneumothorax. These changes tended to disappear in the upright position.

5. A characteristic electrocardiographic pattern is described in our group of left pneumothoraces, with a small T_1, a T_3 larger than T_1, and, in the chest leads, QRS small and inverted, and T waves small or inverted, these chest lead changes being most pronounced in those leads situated farther to the left.

6. We were unable to correlate the electrocardiographic changes with the findings of the chest x-ray films, except for the fact of the presence or absence of air in the pleural cavity.

7. We felt that the cause of the electrocardiographic changes was a combination of displacement of the heart, with an alteration in the electrical field of the heart in relation to the body, and the interposition of a nonconductor (air) between the heart and the chest wall.

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Clinical Reports

NEOPLASTIC INVOLVEMENT OF PERICARDIUM PRODUCING THE SYNDROME OF CONSTRICTIVE PERICARDITIS

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CHRONIC constrictive pericarditis is generally considered to be inflammatory in origin. Most commonly, the infecting agent is unknown or obscure. In a certain number of cases tuberculosis, pneumococcal, staphylococcal, and streptococcal infections have played a causative role. While reports of metastatic tumors of the pericardium are not uncommon, the clinical picture of the syndrome of constrictive pericarditis as a result of this condition is rare, and is, as a rule, not often considered from the clinical point of view.

The following case exemplifies that neoplastic involvement of the pericardium may be the underlying cause of constrictive pericarditis.

CASE REPORT

S. K., a 50-year old laborer, entered Cook County Hospital on Jan. 30, 1946, with complaints of cough, shortness of breath, and weakness. Patient stated that he had felt perfectly well until three weeks before admission, when he developed a cough with expectoration of thick, white mucous, occasionally streaked with blood, and shortness of breath. He also noticed a gradual decrease in appetite, chilly sensations, and night sweats. He felt weak most of the time and complained that after taking about fifty steps he had to sit down and rest on account of weakness and extreme shortness of breath. Occasionally, he experienced a sharp momentary pain over the right costal margin, which radiated to the left breast and was unrelated to effort or ingestion of food. There was no appreciable weight loss. His past history was not especially significant. He had had frequent headaches between the ages of 12 and 14 years, but these disappeared spontaneously without treatment. He denied venereal infection. There was no tuberculosis, hypertension, diabetes, or carcinoma in family. He consumed a moderate amount of beer and whiskey. He smoked one package of cigarettes per day. He did not use coffee or drugs.

Physical examination at this time revealed a well-developed, well-nourished white man who did not appear dyspneic or cyanotic; however, slight movement in bed seemed to cause respiratory distress. His temperature was 98° F.; pulse, 100 per minute and regular; and respirations, 20 per minute. The blood pressure was 108/84. Pupils were round and equal and reacted to light and accommodation. The veins in the neck were slightly distended; no glands were felt in the cervical,

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supraclavicular, or axillary regions. Examination of the chest revealed impaired resonance, over the left upper lobe, anterior and posterior, with a few moist râles over this area. The heart was not enlarged, no murmurs were audible, and the heart tones were somewhat distant. The pulmonic second tone was louder than aortic second tone. The liver was not palpable and no sacral or peripheral edema was noted. There was slight clubbing of the fingers.

Examination of the urine was negative. The hemogram showed 92 per cent hemoglobin, 5,290,000 erythrocytes, 9,200 white blood cells, with 87 per cent polymorphonuclear leucocytes, 7 per cent lymphocytes, and 4 per cent monocytes, and 2 per cent eosinophiles. Five nucleated red blood cells were seen; anisocytosis and polychromatophilia were present. Nonprotein nitrogen was 60 mg. per cent, creatinine 1.9 mg. per cent, and total serum protein 6.8 Gm. per cent. The Kahn test was negative.

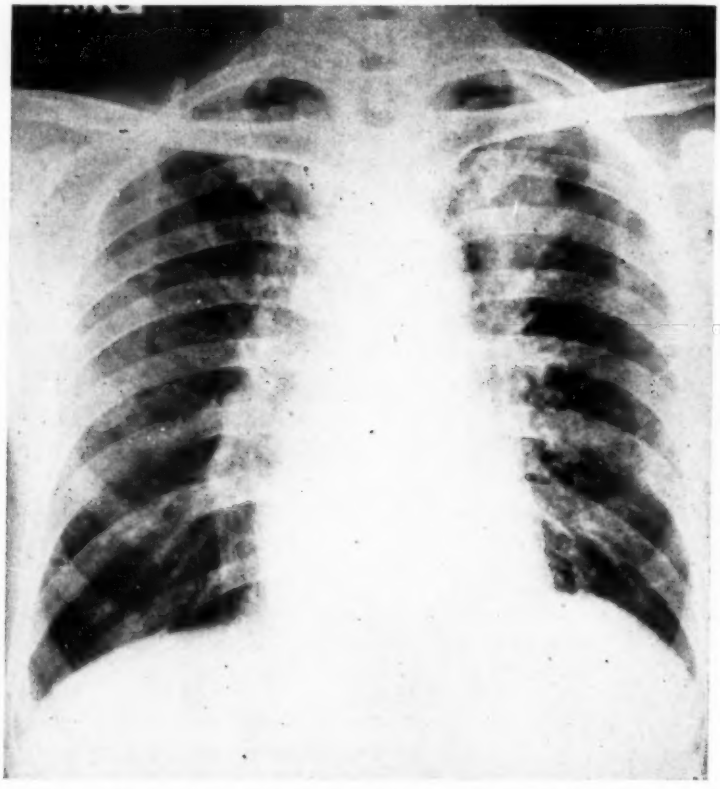

Fig. 1.—X-ray film of chest showing a circumscribed infiltration of the left infraclavicular area. Note the irregular and shaggy outline of the heart shadow.

On x-ray study of the chest (Fig. 1) the cardiothoracic ratio was found to be within normal limits; an irregularity of the contour of the cardiac silhouette was noted with no marked prominence. There was a circumscribed, soft infiltration in the left infraclavicular area, which appeared to communicate with the upper portion of the left hilus area by fibrous strands. No cavitation was noted. The peribronchial markings were accentuated throughout both lung fields. The pulmonary findings were interpreted as being suggestive of possible tuberculosis or carcinoma. Barium meal and enema gave essentially negative findings. Sputum was negative for tuberculosis.

The electrocardiogram showed a sinus rhythm with a rate of 74 per minute. The P-R interval was 0.20 second and the QRS, 0.08 second. P_2 was prominent and notched. The QRS

complexes were of low voltage and upright in Lead I. These complexes were diphasic, but mainly upright in Leads II and III. S-T_2 was slightly depressed. T_2 and T_3 were high and peaked. In Lead IV the QRS complexes were mainly down. T_4 was cove-shaped. These findings were interpreted to be abnormal, but were not considered to be diagnostic of pericarditis.

About one week after admittance to the hospital, there gradually developed cervical vein engorgement, cyanosis of the face and neck, and the liver became palpable three fingerbreadths below the costal margin. The patient developed increasing dyspnea, but no orthopnea, and some ankle edema. The heart rate was now 92 per minute. The apical tones became somewhat more distant, and a paradoxical pulse was noted. At no time was an arrhythmia present. At this point, the change in the clinical manifestations suggested that the density noted in the lung was most likely a malignant process and that the heart was probably secondarily involved by metastasis. Digitalis therapy was instituted, but the patient became progressively worse and showed no response to cardiac management. The patient gradually became more and more lethargic and expired on Feb. 18, 1946, twenty days after admission.

Post-Mortem Findings.—(Autopsy performed four hours after death by Dr. Loeffler.) The abdominal cavity contained 75 c.c. of clear fluid. Dome of diaphragm extended to the sixth rib on both sides. The right pleural cavity contained 50 c.c., the left, 100 c.c. of clear fluid. The apical portion of the left lung was firmly adherent. There were no adhesions on the right side.

The pericardial sac was completely obliterated. The heart was encased by a firm greyish-white tissue which measured up to 12 mm. in thickness. The thickest part was found around the base of the heart and over the entire right ventricle. The cut surface was fascicular in places and granular; it was sharply demarcated from the brownish-red myocardium, which was not invaded. The heart was compressed, but of normal size. There was no hypertrophy of the ventricles. The endocardium and valves were normal.

The apex of the left lung was covered with a nest of adhesions. Just beneath the apex, there was a ball-shaped tumor which was sharply demarcated from the anthracotic lung tissue. It was firm, granular, and traversed by multiple greyish-black lines of connective tissue, which divided the tumor into separate multiple portions. At one point, the tumor reached the mediastinal pleura, which showed here multiple, small, grey nodules. The upper lobe of the right lung was congested but well aerated. Two small tumor nodules were found near the mediastinal pleura, each somewhat smaller than a pea. The base of the lower lobe was atelectatic.

The spleen weighed 140 grams and was firm in consistency. The capsule was thin, the cut surface smooth, and trabeculation accentuated. The liver weighed 1,210 grams. The surface was smooth, the capsule thin, and the cut surface revealed marked chronic congestion with atrophy. There were multiple tumor nodes in both lobes, the largest being the size of a hazelnut. The stomach was dilated. In the duodenum there were three chronic ulcers immediately below the pylorus, each the size of a lentil with radiating folds and formation of a diverticula. Intestines showed marked congestion. Each adrenal contained a metastasis the size of a pea. The kidneys weighed 310 grams. The surface was smooth and light red. The cut surface showed a dark red medulla and a lighter red cortex. The structures were well preserved. Urinary bladder showed a pale mucosa.

Microscopic Findings.—Sections of the pericardium (Fig. 2) show a fibrous stroma containing many glandlike and cleftlike structures lined by cuboidal and elongated cells. In some places, deposits of fibrin can be found. The heart muscle is nowhere invaded.

The large tumor of the lung consists of elongated glandular structures which are separated from each other by broad strands of connective tissue. Also present are hyalinized areas with a large amount of anthracotic pigment. In other places, small narrow cleftlike structures are seen, always surrounded by a thick layer of connective tissue; they are found around and also within arterial blood vessels. In the liver, metastases of same structure are present. On the capsule of each adrenal there are metastases, again consisting of connective tissue and cleftlike structures.

Anatomic Diagnosis.—Primary carcinoma of lung with metastasis to pericardium producing constriction of heart. Metastases to contralateral lung, liver, and adrenals. Chronic congestion of liver, spleen, kidneys, and intestinal tract. Three chronic ulcers of duodenum. Hydrothorax (slight), ascites (slight), and ankle edema (slight).

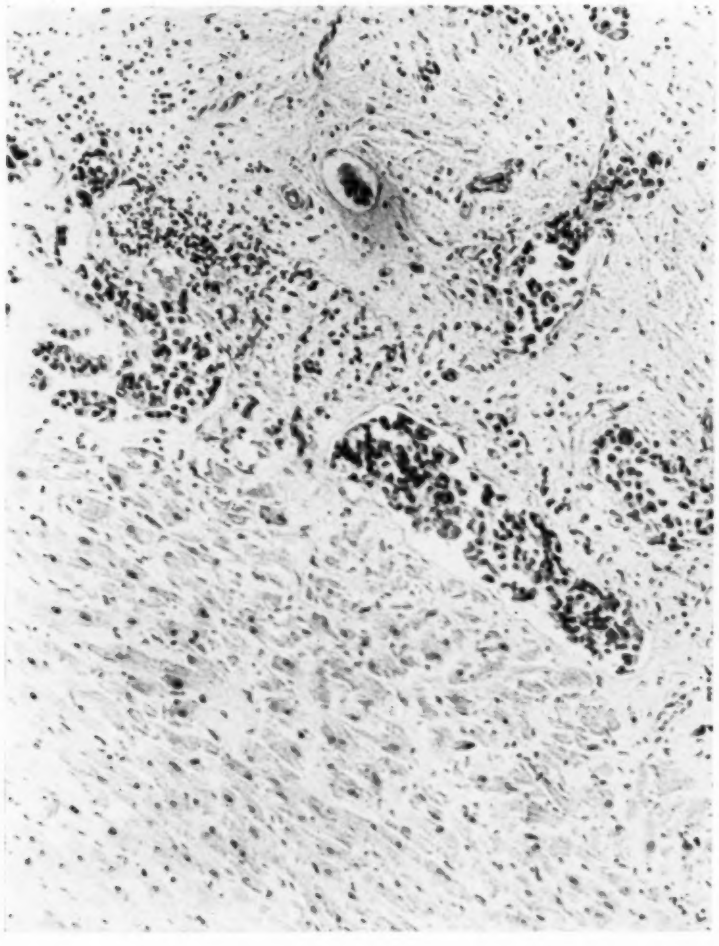

Fig. 2.—Note the cord and glandlike structure of the cancer cells infiltrating the fibrous connective tissue of the pericardium.

DISCUSSION

Tumors of the heart and pericardium are exceedingly rare. Lymburner,[1] in a review of 8,550 autopsies at the Mayo Clinic, found fifty-two cases in which the heart was the secondary site of malignancy. In 1,082 cases of malignant diseases in a series of 11,100 consecutive autopsies at the Cleveland City Hospital, Scott and Garvin[2] found the pericardium involved by metastasis in sixty-one cases. In only one instance was the pericardial cavity obliterated. Pollia and Gogol,[3] in a study of 1,450 malignant tumors, found only twenty-nine secondary tumors of the heart. In 1931 Yater,[4] in a detailed survey of the subject of cardiac tumors, cited eleven cases of neoplasm involving the pericardium and in no case was the pericardial cavity obliterated.

Secondary cardiac involvement may be derived from practically any organ in which malignant disease is to be found. Cardiac involvement has been reported when the primary lesion was in the trachea, lung, stomach, breast, esophagus, kidney, and pancreas. In the majority of instances the primary site, however, was in a bronchus or a breast, and frequently associated pulmonary metastases were found in all reported cases of metastatic carcinoma of the heart.

The mechanism of implantation of tumor cells in the heart must vary considerably. When metastatic growths already exist in the lung, it is conceivable that tumor cells may be swept by the blood stream into the pulmonary vein and eventually reach the coronary arteries and then the smaller branches. The lymphatic supply of the heart and pericardium is exceedingly rich. It must be remembered that the tracheobronchial lymph nodes drain the lung and pleura as well as the myocardium and pericardium and that there may be retrograde invasion of either of these structures. Direct extension from either a primary or secondary tumor in the lung is also possible. In the majority of cases, however, when a malignant tumor is found both in the lung and in the pericardium, it is most logical to assume that the lung tumor was primary and the pericardial tumor metastatic.

The symptomatology of pericardial tumors is variable. There may be no symptoms even though the growth invades the myocardium. This may be due to the fact that the valves are not involved and also to the remarkable degree of reserve possessed by the heart. Yater[4] states that it is astounding how large tumors can become before cardiac function is interfered with. On the other hand, death may occur suddenly with no antecedent symptoms. McDonald[5] reports such a case in which a 53-year-old laborer collapsed while at work and died in a few minutes. At autopsy, pearly white nodules studded the visceral and parietal pericardium. Microscopic study revealed a highly cellular type of tumor.

Usually, however, tumors of the pericardium manifest themselves as pericardial effusions, sanguinous or serosanguinous, or else present themselves as a chronic cardiac compression syndrome,[6,7] such as the case we have described. Hemorrhagic effusion into the pericardial cavity may cause sudden death by acute cardiac tamponade. Mahaim[9] believes that what is most striking about pericardial tumors is the suddenness of appearance of what he terms "mediastinal" signs, such as jugular engorgement, cough, cyanosis, and edema of the upper part of the body. Also, a hemorrhagic pericardial tap, not explainable by other causes, should be considered as possibly due to tumor.

Wallace and Logue[7] state that complete obliteration of the pericardial cavity by tumor is rare and that the production of the syndrome of constrictive pericarditis is even more rare. Lisa and associates[8] emphasize that patients showing evidence of congestive heart failure, refractory to treatment, should be suspected of having cardiac tumors especially if there is no obvious cause for cardiac failure.

Fluoroscopic and roentgen examination is of paramount importance in detecting pericardial invasion. Localized enlargement of the heart, and irregularities or shagginess of contour are suggestive. The introduction of air into the pericardial sac has been recommended as an aid in delineating the presence or absence of tumor.[9] On fluoroscopic examination, the movements of the cardiac borders are diminished. Kymograms may reveal diminution of amplitude of contraction of the cardiac chambers.

The electrocardiographic abnormalities that occur in tumor of the heart are in no way distinctive. However, low amplitude of QRS complexes with RS-T segment changes and subsequent inversion of the T wave in one or more leads is helpful in establishing the diagnosis. Not infrequently an arrythmia such as auricular fibrillation occurs paroxysmally. Rosenbaum and associates[10] reported a case of primary carcinoma of the esophagus with extensive metastases to the heart in which the electrocardiogram showed persistent diplacement of the RS-T segment in Leads II, III, and IV F. The post-mortem observations tended to support the hypothesis that the electrocardiographic changes were due to interference with the blood supply as a result of invasion of the heart by malignant tissue. Mahaim[9] described a bronchogenic carcinoma with extension to the pleura, pericardium, and right auricle, with the electrocardiogram demonstrating nodal rhythm. Autopsy disclosed complete destruction of the sinoauricular node, and thus the A-V node became the pacemaker of the heart. Conduction disturbances may also appear early and Mahaim believes they are often due to vagal effects and occur before actual infiltration of the heart by tumor. In our case the electrocardiogram was not helpful.

SUMMARY

1. Tumors of the pericardium are relatively uncommon and the symptoms are variable.

2. Most cases present themselves as pericardial effusions, usually serosanguinous, or else show signs of myocardial failure terminally.

3. A case is described in which symptoms of constrictive pericarditis appeared somewhat rapidly during the course of a bronchogenic carcinoma and led to the correct diagnosis.

4. When a person has a recognized malignant neoplasm, the onset of symptoms of cardiac dysfunction should suggest metastatic invasion.

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CONGENITAL PULMONARY STENOSIS

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SINCE the number of reported cases of pure pulmonary stenosis constitutes a very small series, we are presenting the history of an additional patient in whom this lesion was found post mortem.

Abbott's[1] series of 1,000 cases of congenital heart disease includes only nine cases of pulmonary stenosis without interventricular septal defect or patent foramen ovale. Currens and associates[2] reported eleven cases of pulmonary stenosis, six of which presented this defect alone. Auerbach and Harper's[3] case showed an associated patent foramen ovale and tricuspid valve deformity. Arnett and Long[4] and Garrison and Feldt[5] reported two additional cases. Maude Abbott,[6] in her Atlas of Congenital Cardiac Disease, presented two instances of pulmonary stenosis remarkable in that the stenosis was below the pulmonary valve at the lower bulbar orifice. Freed and Budnitz[7] have recently described one case of pure pulmonary stenosis. The case which we wish to add to the literature of this interesting condition will be presented.

CASE PRESENTATION

The patient was an 11-year-old girl who, on initial examination, did not appear acutely ill. The body build was sthenic with normal feminine contours. The cheeks were flushed with a cyanotic tinge. The hands and feet were quite white, with a deep pinkish-purple discoloration of the distal phalanges of the fingers and toes. There was marked underdevelopment of all the distal phalanges but no clubbing was present. The lower extremities were quite cool to the touch. A mottled cyanosis was evident on the thighs.

Examination of the heart showed a rate of 100 per minute with regular rhythm. No thrills were elicited. The cardiac impulse was heaving in character and was felt plainly in the third left intercostal space at both the midclavicular and the anterior axillary lines. The apex impulse could also be felt in the sixth intercostal space at the midaxillary line. Auscultation revealed a systolic blow heard over the whole chest, anteriorly and posteriorly. The percussion note was dull over the whole left anterior chest as high as the second rib and laterally as far as the midaxillary line. No breath sounds were heard over the left anterior chest except below the level of the sixth rib in the midaxillary line and above the second intercostal space. Over the other portion of the lungs, breath sounds and resonance were normal and no râles were heard.

The electrocardiogram (Fig. 1) showed a marked right axis deviation.

X-ray findings (Fig. 2) at the time of the original examination showed normal lung fields. There was definite evidence of prominent hilar vessel markings on the right side; the left hilus was obscured by heart shadow. The heart shadow showed evidence of gross enlargement; there

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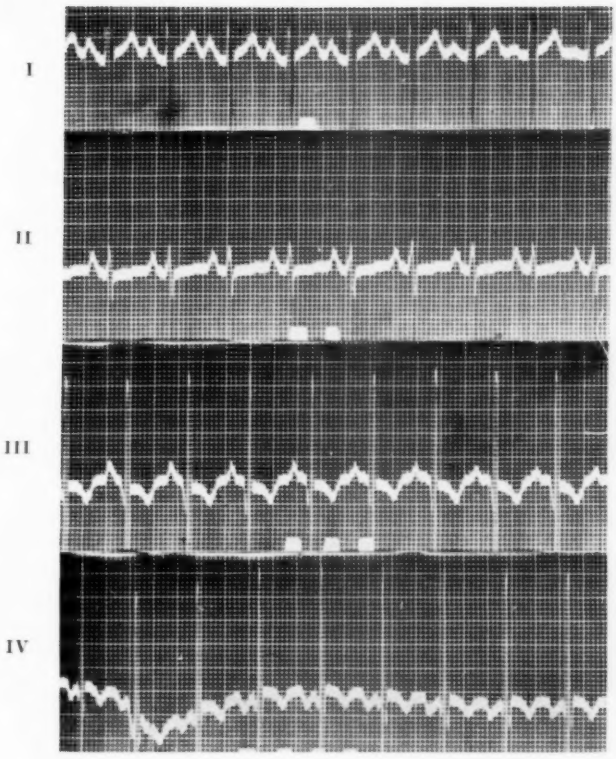

Fig. 1.—Electrocardiogram consisting of three standard leads and Lead IV taken Jan. 24, 1944. The tracing shows a marked right axis deviation.

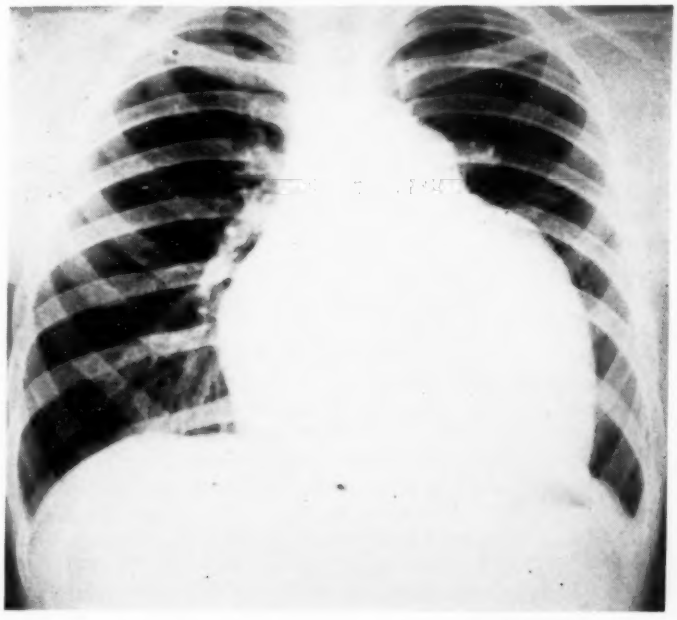

Fig. 2.—X-ray film of heart and lungs made Jan. 24, 1944. The total diameter of the heart is increased and the pulmonary artery is very prominent.

was marked prominence of the pulmonary conus. The left heart border showed evidence of marked elevation, this contour forming a deep angle with the left diaphragmatic contour. The outline of the right auricle was enlarged. The heart measurements were: median right, 4.8 cm.; median left, 11.4 cm.; total transverse diameter, 16.2 cm.; and total internal thoracic diameter, 27 centimeters. The cardiothoracic ratio was 0.60. The left lateral border of the pulmonary conus was approximately 5.5 cm. to the left of the midline. The roentgenologic diagnosis was congenital pulmonary stenosis without evidence of cardiac decompensation.

The history revealed that a heart murmur had first been found at the time of the patient's entrance into kindergarten. She had never been able to play as actively as a normal child and had always complained of excessive fatigue. At the time she was first seen, a walk of even one block required rest, and climbing one flight of stairs produced dyspnea. No chronic cough, fainting, or chest pain had been present.

The patient had been forced to leave school a few months before she was first seen at our office, because the exertion required to reach school (one block away) was too much for her. On subsequent examination, increasing weakness and fatigue were noted. On one occasion, the blood pressure was 100/50 in the right arm and 90/50 in the left arm. A thrill became apparent in the left first, second, and fourth intercostal spaces just to the left of the sternum, and slight cyanosis of the lips appeared. Another blood pressure reading was: right arm, 130/80; left arm, 120/90. Bed rest was continued.

The gradual downhill course continued with the appearance of dyspnea and cold sweat if the patient arose from bed. It seemed that the heart was increasing in size and an apparent bulge was noted over the left second and third intercostal spaces.

In November, 1945, the patient was hospitalized for three weeks because of marked dyspnea, edema of the ankles, and cardiac pain. The heart rate ranged from around 120 to 140 per minute. Even though blood cultures were negative, penicillin was given in view of her continued fever, which ranged around 100° Fahrenheit. Purodigin was given and the patient finally improved. On dismissal, her heart rate was 88 to 92, breathing was easier, pain in the heart was less, and there was no decompensation. Urinalysis during this hospital stay showed 4 plus albumin, a few red blood cells, and a few pus cells.

The heart rate gradually increased but never returned to 120, which was her previous consistent rate. There was increasing edema of the feet and ankles, and later, marked edema of the sacrum, thighs, and vulva. The heart rate continued around 90 to 100 per minute, with occasional extrasystoles. Nausea recurred, at which point digitalis was omitted. The edema improved considerably following injections of Salyrgan.

On Jan. 6, 1946, when seen at home, the patient complained of heart pain and dyspnea, and was very restless. The face showed cyanotic blotches where previously there had been bright pink, slightly cyanotic spots on her cheeks. The extremities were cold and cyanotic. The heart showed frequent extrasystoles and finally a slow auricular fibrillation with a slow ventricular rate. A moderate ascites was present. That evening the patient suddenly developed extreme dyspnea and died within ten minutes.

Necropsy.—There was pronounced edema of the dependent portions of the body; edema of the thighs was present, and even the tissues of the thorax were waterlogged. Prominent cyannosis of the face and extremities was noted.

Exposure of the pericardial sac showed that the heart was bulging and large. Like the other tissues, it presented a cyanotic appearance. As the heart lay in situ, the left chambers were not visible from the front because of the tremendous enlargement of the right chambers. The pulmonary conus was prominent. The pericardium was smooth and glistening and contained a normal amount of pericardial fluid. The vessels attached to the heart revealed no abnormality. The pulmonary artery and the aorta were in normal relation to each other, and normal in diameter. There was no communication between the vessels, the ductus arteriosus being definitely closed and the scar demonstrable. It was estimated that the heart weighed 600 grams.

The interior of the right ventricle presented marked hypertrophy of the papillary muscles. No scarring of the muscle was noted, although there was marked irregular streaking with fat throughout the myocardium. The right ventricular wall and the conus arteriosus measured up

to 2.2 cm. in thickness; whereas the left ventricular wall measured up to 1 to 1.2 cm. in thickness. The capacity of the right chambers was increased, that of the right auricle being approximately 300 c.c. and the right ventricle 150 cubic centimeters. The foramen ovale was completely obliterated by old scar and there was no communication between the ventricles.

Fig. 3.—Necropsy specimen. There is marked stenosis of the pulmonary valve.

Inspection of the valves showed the tricuspid valve to be 15 mm. in circumference. Except for the increased size of the tricuspid, valve changes were restricted to the pulmonary valve, which presented a marked stenosis (Fig. 3). The three cusps were distinctly outlined but fused along their edges, except for a small opening 2.0 mm. in diameter in the center of the valve orifice. The valve ring, however, was of normal caliber. The valve cusps were moderately thicker than usual but there was no marked fibrosis and they retained their usual pliability. Inspection revealed no deformity other than the stenosis of the pulmonary valve, which was a pure lesion in this case.

SUMMARY

A case is presented in which marked stenosis of the pulmonary valve was the only primary cardiac lesion present.

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ERRATUM

The article entitled "Experience With Three Vascular Fragility Tests in Hypertension," by John Schweppe, M.D., Howard A. Lindberg M.D., and the late N. Herbert Barker, M.D., AM. HEART J. **35**:393 (March), 1948, contained an error which must be corrected. In the last line of the first paragraph on page 399, it stated that "the blood cyanate was 100 mg. per cent." This figure should have been 10 mg. per cent.

Abstracts and Reviews

Selected Abstracts

Cabrera, E. C., and Sodi-Pallares, D.: El Gradiente Ventricular y el Componente Anormal en el Diagnostico de los Infartos del Miocardio. Arch. Inst. cardiol. México **17**:356 (June), 1947.

The information to be derived from the ventricular gradient and its limitations are studied from a theoretical point of view in the isolated muscle as well as in the human heart. Considering that the normal human heart has a given ventricular gradient, an abnormal ventricular gradient does not indicate by itself the location of a myocardial abnormality in the human being. An abnormal ventricular gradient can be considered as the vectorial resultant of a normal component (original normal gradient) plus an abnormal component (represented by a vector uniting the ends of both ventricular gradients).

In the human heart, the study of the abnormal component seems to have a closer correlation with the gradient of anatomic or physiologic abnormality than does the ventricular gradient itself.

Five cases were chosen from the medical literature to illustrate the advantages of using the abnormal component in the study of myocardial infarction.

When the electrocardiogram shows evidence of a zone of injury, the vectorial study becomes complicated: During diastole the potential gradient produced by an injured zone has the same direction as the gradient of anatomic and/or physiologic abnormality, whereas during systole the electrical effects disappear or are reversed.

Since only during systole we can study the electrocardiographic effects of an injured zone, the direction usually assigned to the potential gradient produced by the injured zone is diametrically opposed to the one it actually has, and therefore cannot be correlated with the gradient of anatomic and/or physiologic abnormality. This is the reason we do not feel that it is a sound procedure to include the areas of the RS-T segment in the calculation of the ventricular gradient when the electrocardiogram shows evidence of a zone of injury.

We feel that it is very useful to study both the normal and abnormal components of the cardiac vectors (A_{QRS}, A_T, and G) in every case of myocardial ischemia or infarction.

AUTHORS.

Hingston, R. A., and Southworth, J. L.: The Use of Continuous Caudal and Continuous Spinal Analgesia in the Diagnosis, Prognosis, and Rehabilitation of the Peripheral Vascular Diseases of the Lower Extremities. Mil. Surgeon **100**:474 (June), 1947.

The authors attempted to evaluate the use of various procedures for the temporary and permanent removal of vasomotor tonus to the vessels of the extremities as therapy in peripheral vascular disorders. They utilized continuous caudal analgesia with 1.5 per cent metycaine, continuous spinal anesthesia using a ureteral catheter, paravertebral sympathetic nerve block, and sympathectomy.

In the case of acute arterial insufficiency produced by trauma to the large vessels in an extremity, they found continuous spinal anesthesia, caudal analgesia, and sympathetic block of value in producing vasodilatation of the remaining intact arterial tree, thus providing sufficient collateral circulation to maintain nutrition of the entire extremity or to make possible a more peripheral amputation. The authors concluded that sympathetic denervation should be used

in all cases in which there is any hope of a viable extremity. They pointed out, however, that not all workers in the field hold this opinion. In the presence of spasm or thrombosis of a major artery, removal of vasomotor tonus by paravertebral block, by the use of alcohol, or by other procedures also produced a beneficial response.

In chronic arterial insufficiency, as thromboangiitis obliterans, ulceration of toes was helped by temporary or permanent sympathetic denervation, while burning pain of the sole and rest pain were not particularly relieved by such a procedure. On the other hand, exercise tolerance was increased. However, it was pointed out by the authors that the use of sympathectomy is not without danger in thromboangiitis obliterans.

The advantage of repeated paravertebral blocks in overcoming vasospasm that exists in the initial stage of acute deep thrombophlebitis and that is also responsible for some of the sequalae of immersion foot and trench foot was emphasized. However, in the case of the latter two conditions, only in certain types of patients was removal of vasomotor tonus found to be useful.

ABRAMSON.

Laudin, H. C.: Electrocardiogram and State of Physical Condition. Deutsche med. Wchnschr. (June 6), 1947.

The author states that in previous publications he has repeatedly pointed to the fact that heart function tests with spirograph and ergometer have shown that mildly decompensated cardiac patients and untrained healthy persons, not conditioned by exercise, can show similar pathologic deviations. It is, therefore, important to be able to separate mild cardiac complaints due to organic damage from complaints due to lack of training or physical conditioning. He cites the work of others who found both P-Q and Q-T intervals prolonged at rest and shortened on effort in those persons long accustomed to rigid athletic training or occupied in heavy manual labor.

Healthy students were exercised for twenty minutes daily with an ergometer producing 150 watts for a period of three months. Concomitant spirographic readings showed that the persons thus tested at the end of the three-month period required hardly two-thirds of the respiratory volume needed at the beginning of the period. Electrocardiographic tracings were taken at rest and immediately following exercise, before the test was started, every ten days afterward, and again after the three-month period. A group of well-conditioned, average athletes was also tested in the same fashion, using an ergometer producing 200 watts.

No prolongation of P-Q or of Q-T intervals was noted in the group of students tested and no more than 2 to 3 per cent showed prolongation among the group of average athletes.

The author draws the conclusion that an average or good state of physical conditioning occasions no changes in the electrocardiogram. It is important to know the actual state of physical conditioning of an individual in order to decide whether cardiac complaints are due to organic damage.

KRAMER.

Miller, R. A., Heagan, B. S., and Taylor, B. C.: The Oxygen Content of Arterial Blood in Dogs Breathing Air at Low Barometric Pressures. Am. J. Physiol. **150**:1 (July), 1947.

The average arterial oxygen saturation of eight dogs at ground level (750 feet) was 95.26 per cent. These dogs were then exposed to simulated altitudes of from 5,000 to 35,000 feet for sixteen to forty-nine minutes. The average saturation decreased from 87.43 per cent at 5,000 feet to 24.68 per cent at 35,000 feet. The carbon dioxide content of whole blood fell from 39.77 volumes per cent at 5,000 feet to 12.42 volumes per cent at 35,000 feet. The arterial oxygen saturation and length of consciousness are compared in dogs and in man and reveal that dogs retain consciousness for a much longer time than does man, even though the arterial oxygen saturation of dogs is 9 to 16 per cent lower than that of man at altitudes between 5,000 and 22,000 feet.

BERNSTEIN.

Britton, S. W., Pertzoff, V. A., French, C. R., and Kline, R. F.: Circulatory and Cerebral Changes and Protective Aids During Exposure to Acceleratory Forces. Am. J. Physiol. **150**:7 (July), 1947.

Using a 20-foot diameter heavy steel centrifuge with blood pressure and other devices attached for determining effects of accelerations up to 50 g, the results of tests on a large number of monkeys, dogs, and cats were determined. Electrocardiographic records from the left precordium (a modified Lead IV) showed marked voltage reduction of the R and S waves recorded at left precordial positions during positive g exposure and increase in voltage when the right chest record was obtained simultaneously. This was shown to be due to heart position and blood content. Arterial pressure changes (carotid, brachial, femoral) showed a linear relationship to applied g stresses and a carotid sinus reflex response affecting arterial pressure appears to be initiated six to eight seconds after starting exposure to high g forces. Blood flow reductions in the carotid artery occurred within a second or so after starting the centrifuge. Under a force of 3 or 4 g for ten seconds, flow in the carotid artery usually reached the zero level. Attempts to produce conditioned reflex responses and "experimental neurosis" by exposure to high g forces were unsuccessful. Considerable protection against g forces was afforded by a belt or cuff around the abdominal area inflated usually up to 300 mm. Hg pressure. The advantage afforded by abdominal belt pressure varied between 1 and 3 g inversely to the severity of the exposure. Adrenalin gave moderate and very brief protection.

BERNSTEIN.

Ralston, H. J., Taylor, A. N., and Elliott, H. W.: Further Studies on Streamline Blood Flow in the Arteries of the Cat. Am. J. Physiol. **150**:52 (July), 1947.

The importance of recognizing the dynamic pattern of the blood flow in studies on the circulation is emphasized. Observations of the movements of particles of ink in a glass tube inserted into the lower abdominal aorta of the cat shows that the flow is streamlined under the conditions of the experiment. A retrograde movement of the blood during a brief portion of the cardiac cycle was confirmed and evidence is given that ink injected into the root of the aorta or into the descending thoracic aorta may be unequally distributed to tributary arteries. These findings are consistent with earlier evidence for laminar flow in the aorta. Individual particles of ink do not exhibit radial motion except under conditions of obvious turbulence, such as when a thrombus forms in a glass segment, resulting in a violent eddy formation.

BERNSTEIN.

Hertzman, A. B., Randall, W. C., and Jochim, K. E.: Relations Between Cutaneous Blood Flow and Blood Content in the Finger Pad, Forearm, and Forehead. Am. J. Physiol. **150**:122 (July), 1947.

The unreliability of depending upon the intensity of skin color as a determination of blood content in the subpapillary venous plexus in the estimation of skin flow is discussed. The estimation of the quantity of blood in the minute vessels of the skin is also discussed and calculations presented to show that the total quantity of blood normally present in these vessels is relatively small. The use of a photoelectric plethysmograph for the estimation of the blood content and blood flow in the skin is described and analyzed.

BERNSTEIN.

Keys, A., Henschel, A., and Taylor, H. L.: The Size and Function of the Human Heart at Rest in Semistarvation and in Subsequent Rehabilitation. Am. J. Physiol. **150**:153 (July), 1947.

Measurements of the heart and its functions were made on thirty-two normal young men in rest before, during, and after six months of semistarvation in which one-fourth of the body weight was lost. During semistarvation the heart decreased in all dimensions and assumed a more upright position in the chest. The total volume reduction averaged 16 per cent and the stroke volume reduction averaged 18 per cent. The venous pressure was not more than 50 per

cent of the normal level. There was a marked tendency toward bradycardia with cyanosis of the nail beds, but no dyspnea. The margin of safety represented by the ratio of metabolism to the oxygen circulated in the blood fell to one-half the normal average.

In the first three months of rehabilitation on controlled diets, the heart size returned to the control level but other characteristics of cardiac function showed recovery which was generally somewhat less in proportion to the recovery of lost body weight (vitamin or protein supplementation had no significant effects on the recovery of cardiovascular function). After twenty weeks of rehabilitation, the work done by the heart was still about 10 per cent below the control, and only one-half of the lost margin of safety had been restored. There were signs that the heart was closer to failure in early rehabilitation than in starvation (stroke output of diastolic heart volume decreased compared with both control and semistarvation values). One case of congestive failure in rehabilitation responded promptly to conservative management.

BERNSTEIN.

Harpuder, K., Byer, J., and Stein, I. D.: The Effect of Intra-Arterial Injection of Adrenalin Upon Blood Flow of the Human Forearm. Am. J. Physiol. **150**:181 (July), 1947.

Blood flow in the human forearm was studied by the plethysmograph method. Injection of adrenalin in doses of 1 to 2 gamma into the brachial artery produces vasoconstriction while doses of 0.5 to 0.1 gamma are ineffective. Intra-arterial doses of 0.05 to 0.0002 gamma cause vasodilatation sometimes followed by vasoconstriction; 0.00002 gamma seems to be the threshold of vasodilator action. The authors believe that this indicates a double action of adrenalin on a constrictor and dilator mechanism, one system or the other predominating depending upon the adrenalin concentration. Such studies are of clinical importance in view of the present tendency to perform sympathectomies rather liberally.

BERNSTEIN.

Haynes, F. W., and Dexter, L.: Renin, Hypertensinogen, and Hypertensinase Concentration of Blood of Dogs During the Development of Hypertension by Constriction of the Renal Artery. Am. J. Physiol. **150**:190 (July), 1947.

In ten dogs, the renal artery was clamped by means of a Goldblatt clamp which was screwed down to occlude the vessel and then turned back about three-fourths of a turn. During the development of experimental renal hypertension, renin was detected in the plasma, which reached a maximum about one week after both renal arteries were constricted and then gradually subsided. A rise in the nonprotein nitrogen was not necessarily present with this increased renin. Hypertensinogen remained unchanged or increased in the plasma unless the renin became excessive, in which case the hypertensinogen concentration decreased. The authors admit that present methods may be too insensitive to detect renin in chronic hypertension and also that it is possible that the renin system has nothing to do with the development and maintenance of experimental renal hypertension and that its production is determined by autolysis of kidney tissue.

BERNSTEIN.

Haynes, F. W., Dexter, L., and Seibel, R. E.: Renin Content of Renal Venous Blood of Normal and Hypertensive Patients at Rest. Am. J. Physiol. **150**:198 (July), 1947.

In this experiment, the renal vein was catheterized by a catheter directed fluoroscopically, and its position checked before and after withdrawal of the blood sample. Renin was detected in the renal venous blood in approximately the same amount and with the same frequency in a group of twelve hypertensive patients and in a group of twelve patients with normal blood pressures at rest. In the hypertensive group, there was no relation between the severity or etiology of the hypertension and the concentration of renin in the renal venous blood. Such findings do not support the hypothesis that renin is the humoral substance responsible for human hypertension.

BERNSTEIN.

Bartelheinich, M.: Peculiarities of the Circulatory System in Acromegaly. Deutsche med. Wchnschr. (July), 1947.

The author made a study of the circulation in twenty-one cases of the acromegalic syndrome. Eight patients showed the typical endocrine picture of acromegaly; the remaining thirteen showed definite evidence of peripheral growth but not the full-blown classical symptomatology.

Although it has long been known that the heart can become considerably enlarged as part of a generalized splanchnomegaly, the author observed that there were also other very important evidences of disturbance in the circulatory mechanism which have received little attention. Thus, fourteen of the twenty-one cases investigated showed evidence of myocardial damage in the electrocardiogram. This was relatively more frequent and more advanced in those who showed the classic endocrine picture than in those who showed the less well-developed symptomatology. The conclusion is drawn that myocardial damage is dependent on the extent of the hyperfunction of the eosinophile portion of the anterior pituitary lobe.

Hypertension, frequently observed in the twenty-one cases investigated, does not belong to the picture of acromegaly but is due to concomitant hyperfunction of the basophile portion of the anterior pituitary lobe. The precocious occurrence of arteriosclerosis and peripheral circulatory disturbances is also frequently found in acromegaly and is said to be dependent on the dysfunction of the autonomic nervous system.

KRAMER.

Giunchi, G.: Contribution to the Study of Penicillin Action in Subacute Bacterial Endocarditis. Cuore e circolaz. **31**:125 (July-Aug.), 1947.

A case of subacute bacterial endocarditis with positive blood culture for *Streptococcus viridans* was treated with penicillin. The dose of penicillin was initially 240,000 units, then 800,000, and later 1,000,000 units per day. After three weeks under the last dose and after repeated negative blood cultures, severe multiple embolization occurred during which the blood culture again became positive. The patient later received 1,000,000 units of penicillin daily for five days and every sign of the disease disappeared. In spite of the subsequent discontinuance of the treatment, caused by lack of the drug, apparently complete recovery occurred and the patient returned to work three months later. The fact that the organisms at first seemed to be resistant in vivo (not in vitro) and later were destroyed only five days after a severe embolization with positive blood culture is explained in the following way: a focus of infection was present in the mitral valve; its destruction, which caused embolization, permitted better contact between penicillin and the infecting organisms and led to apparent cure of the infection.

LUISADA.

Friedman, M.: Studies Concerning the Etiology and Pathogenesis of Neurocirculatory Asthenia, V. The Introduction of a New Test for the Diagnosis and Assessment of the Syndrome. Psychosom. Med. **9**:233 (July-Aug.), 1947.

The author devised a ventilation test, preceded and followed by maximum breath holding, which gave some semblance of quantitation and standardization. Thirty normal adults were selected for the determination of breath-holding time before and after a period of hyperventilation. It was found that each of the thirty subjects were able to hold their breath considerably longer after hyperventilation than before. The average hyperventilation index (H.I.) was 1.58 (range: 1.30 to 2.13). Thirty-four patients with neurocirculatory asthenia with easily induced dyspnea, together with five patients with neurocirculatory asthenia who were not dyspneic, were given the test. The five nondyspneic patients were able to hold their breath for a normal length of time and the average hyperventilation index was 1.50. When the thirty-four patients with easily induced dyspnea were given the test, it was found that their breath-holding time was significantly lower than that of the control group. Thirty-three of the thirty-four patients had a hyperventilation index of less than 1.30. From these observations, it is seen that the severely dyspneic patients not only showed less gains in breath holding after hyperventilation than the control patients, but were unable in many instances to hold their breath as long after hyperventilation as they had been able to do before hyperventilation. It was also found that the smaller the hyperventilation index, the more severely ill the patient appeared.

Ten young adults suffering from dyspnea and palpitation on moderate exertion and showing evidence of organic heart disease were subjected to the test. None of the ten exhibited manifestations of neurocirculatory asthenia or acute congestive failure. Each of the ten gained normally in breath holding after hyperventilation, their average hyperventilation index was 1.57. Seven adults with organic heart disease, with signs of neurocirculatory asthenia, were given the hyperventilation test. It was found that the average initial breath holding time was greater than that attained after hyperventilation, the average hyperventilation index was 0.90. Twenty patients suffering from traumatic pneumothorax or hemopneumothorax, advanced pulmonary tuberculosis, or allergic asthma were given the test. It was found that the relative gain in breath holding after hyperventilation was approximately the same as that found in normal subjects. The hyperventilation index averaged 1.57 in the first group, 1.50 in the second, and 1.57 in the last group. Five patients suffering from bronchial asthma were given the test and it was found that each of the five failed to gain in breath holding after hyperventilation. The average hyperventilation index was 0.71.

The test and the index obtained from it are presented not only as a positive diagnostic method for the detection of severe neurocirculatory asthenia but also as a method for the assessment and differentiation of the part played by the neurocirculatory asthenia syndrome in the production of cardiorespiratory symptoms in patients who suffer from both this syndrome and organic cardiorespiratory disease.

BELLET.

Friedman, M.: Studies Concerning the Etiology and Pathogenesis of Neurocirculatory Asthenia, VI. Episodic Neurogenic Discharge as a Manifestation of the Syndrome. Psychosom. Med. 9:242 (July-Aug.), 1947.

The frequency, pathogenesis, and nature of episodic neurogenic attacks were studied in sixty-two patients with neurocirculatory asthenia. These attacks were characterized by syncope and cardiovascular, respiratory, and peripheral neurogenic dysfunction. The sixty-two hospitalized patients were observed for an average period of twenty-six days. The average age was 24 years. Forty-eight of the patients (77 per cent) experienced, at some time during their hospital stay, an attack of episodic neurogenic discharge.

The predominantly cardiovascular type was the type most frequently observed and occurred in twenty-eight patients. The average attack began abruptly. An arrhythmia was observed in sixteen of the twenty-eight patients having a discharge. The remaining twelve patients were observed to have regular rhythm but extraordinarily forceful and rapid contraction of the heart. Besides the cardiac manifestations, the patients also exhibited an accentuation of pre-existing hand tremor, excessive sudation, and cold, moist hands. The duration of this type of discharge varied from several minutes to several hours. The sixteen patients presenting this type of discharge were typical examples of hyperventilation syndrome. The original impulse for the pathogenesis of this type of discharge was of psychogenic or neurogenic origin.

Four of the patients of the entire series were observed to exhibit a peripheral neurogenic type of discharge. Only two of the sixty-two patients actually lost consciousness frequently. It was found that syncope could be produced in these patients by massage of either the right or left carotid sinus, and unconsciousness occurred without observable change in either pulse rate or blood pressure. After consciousness was regained, it was observed that they became highly emotional without actually having had any discernible cause for an emotional reaction. The ease with which the syncope could be brought about was not dependent upon the posture of the patient's body but upon the position of his head in space.

BELLET.

Dolger, H.: Clinical Evaluation of Vascular Damage in Diabetes Mellitus. J.A.M.A. 134:1289 (Aug. 16), 1947.

Two hundred patients in whom the onset of diabetes occurred before the age of 50 years, either in childhood, adolescence, or adulthood, were the subjects of this study. Fifty-five were juvenile patients in whom the diabetic condition began before the age of 20 years. The infre-

quency of significant vascular damage in nondiabetic persons of this age obviated the need for a comparison group.

The fifty-five juvenile patients included ten whose diabetes began before the tenth year. There have been seven fatalities among the fifty-five cases. The treatment of twenty young diabetic patients satisfied all orthodox criteria for excellent diabetic control. Retinal hemorrhages were noted in all twenty patients; the average duration of diabetes was thirteen years when the earliest retinal lesions were observed, the extremes being six and twenty-two years. By the time retinopathy had developed, 50 per cent of patients presented definite hypertension and 30 per cent, albuminuria. A parallel group of eighteen patients in whom only a fair degree of diabetic control could be obtained presented retinal hemorrhages within five to twenty years after onset, the average duration of diabetes for this group being 10.4 years. At this time, one-third of the eighteen patients displayed hypertension and albuminuria. A third group of seventeen patients had an unusually severe form of diabetes in which glycosuria and hyperglycemia defied all therapeutic measures. A free diet was condoned in these cases. The incidence of retinal hemorrhage was noted between five to nineteen years after the onset of diabetes, an average group span of 12.4 years.

In the group between the ages of 20 and 29 years, the appearance of retinal hemorrhage was noted between four and twenty-two years after the onset of diabetes. In the group 30 to 39 years of age, retinopathy appeared between three and twenty-four years after the onset of diabetes. The patients in these two decades presented almost identical association of hypertension and albuminuria in about 50 per cent of cases. The oldest group, 40 to 49 years of age, presented evidence of accelerated vascular degeneration with the earlier appearance of all the abnormal findings. The retinal lesions were noted between zero and twenty years after the onset of the disease. Several patients showed advanced visual failure even before the classic symptoms of diabetes appeared.

The appearance of retinal hemorrhage often presaged the inevitable pattern of more generalized and progressive vascular degeneration. Twenty-seven patients of the total group of 200 became partially or totally blind. The duration of diabetes in these cases was fourteen years in two instances and sixteen, nineteen, and twenty-four years in the others. These five patients presented the triad of the originally described syndrome of hypertension, albuminuria, and nephrotic edema.

The most significant deduction to be drawn from this study is that the duration of the diabetes mellitus rather than the method of treatment is the most important factor in the development of degenerative changes.

BELLET.

Malmstrom, G.: The Cardiological Anoxemia Test With Special Reference to Its Standardization. Acta med. Scandinav. Suppl. 195, 1947.

An attempt is made to provide further information on alveolar ventilation, alveolar and arterial oxygen saturation, plasma pH, and electrocardiograms during short periods of induced anoxemic anoxia in normal subjects and in patients with arteriosclerotic heart disease. The material is divided in four groups. The first consists of forty-one normal subjects, 19 to 30 years of age; the second, of ten healthy individuals between the ages of 40 and 59 years; the third, of twelve patients from 40 to 65 years of age, with possible angina pectoris; and the fourth, of twelve individuals, 40 to 70 years of age, with definite angina on effort. The anoxic period was carried for not more than fifteen minutes. In the normal group two mixtures were compared, one consisting of 9 per cent oxygen and the other of 4.5 per cent carbon dioxide and 6.5 oxygen in nitrogen. Examples of suspected or overt coronary artery disease were tested with the second mixture only.

Alveolar ventilation as determined from depth of inspiration, dead space, and respiratory rate was of course greater in mixtures containing carbon dioxide, and the individual variations were smaller. The addition of carbon dioxide, therefore, reduced one important variant. Arterial oxygen saturation was slightly lower in the 9 per cent oxygen mixture. Little difference in oxygen saturation at five and at fifteen minutes was present in those receiving the 6.5 per cent oxygen-carbon dioxide mixture, while those receiving the 9 per cent oxygen mixture showed a gradual de-

crease throughout the test, although near maximal values were established within the first few minutes. (Oxygen values were determined gasometrically.) The pH of plasma was slightly more alkaline on 9 percent oxygen (7.59) than on the low oxygen-carbon dioxide mixture (7.49). (Gasometric determination and potentiometer readings using a glass electrode.) Again the dispersion of values was less on the carbon dioxide-oxygen mixture.

The blood pressure fell a few points when the 9 per cent mixture was used but remained stationary on the low oxygen-carbon dioxide mixture. A precipitous drop in pressure occurred in five of 31 patients on 9 per cent oxygen and in one of forty-six patients on the second mixture, necessitating the termination of the test. Electrocardiographic standard limb leads and Lead IVF revealed changes compatible with Levy's observations.

It is argued that the addition of carbon dioxide to the gas mixture enhances the usefulness of the test by providing a more uniform response in human subjects.

HECHT.

Torrini, A.: Congenital Heart Disease With Terminal Cerebral Abscess Simulating Subacute Bacterial Endocarditis. La Settimana Med. **2:**312 (Nov.) 1946.

A 26-year-old woman with patent ductus arteriosus and coarctation of the aorta presented a clinical picture of sepsis which was diagnosed as bacterial endocarditis. Autopsy revealed the existence of an abscess in the occipital lobe. The occurrence of the cerebral abscess was considered as connected with the heart disease.

LUISADA.

Capellini, A., and Brigatti, L.: The Electrocardiogram in Silicosis. La Med. del Lavoro **38:** 47 (Feb.), 1947.

The authors studied the electrocardiographic tracings of 150 patients with pulmonary silicosis in various stages. In nine patients, evidence of moderate myocardial damage was found, as shown by high take-off and changes of the T wave. Auricular fibrillation was present in one subject. Comparison of the electrical axis with the configuration of the chest indicated an increased proportion of right axis deviation. This was more frequent in those cases manifesting a nodular type of lesion or extensive and diffuse silicosis.

LUISADA.

Schlesinger, P., and Cotrim, M. R.: Transient Auricular Fibrillation Caused by Digitalis. Arq. de Clin. **4:**167 (March), 1947.

Six cases manifesting transient auricular fibrillation after digitalis administration were studied. The conditions frequently associated with auricular fibrillation, mitral stenosis and thyrotoxicosis, were absent. Some of the patients developed auricular fibrillation early in the course of digitalization, which was accompanied by a rapid heart rate and a severe heart failure. Others developed auricular fibrillation only after toxic doses of the drug.

The onset of auricular fibrillation in patients receiving digitalis should be considered as an indication to discontinue its administration.

LUISADA.

Benchimol, A. B., and Cotrim, M. R.: Beri-beri Heart. Arq. de Clin. **4:**181 (March), 1947.

A patient living in Rio de Janeiro presented typical signs of beri-beri heart disease with severe heart failure. The existence of heart failure together with an extremely rapid circulation time and the signs of multiple vitamin deficiency (polyneuritis, pellagra, cheilitis, and psychic disorders) facilitated the diagnosis. Treatment with vitamin B-complex was followed by recovery of the patient. The electrocardiographic signs (low voltage of the T wave) and the x-ray findings (enlargement of the heart with pulmonary and hilar congestion) disappeared after treatment.

LUISADA.

Taquini, A. C., and Fasciolo, J. C.: Dosage of Circulating Renin in Arterial Hypertension. Rev. argent. de cardiol. **14**:1 (March-April), 1947.

A new method capable of detecting small quanitities of renin (as little as 5×10^{-4} units per cubic centimeter of plasma) was used for renin determination in the blood of normal dogs, in dogs with experimental renal hypertension, in normal subjects, and in patients with arterial hypertension of various etiologies.

Small amounts of renin were detected in all dogs and human subjects, irrespective of their blood pressure, and no difference in the serum level was found. The conclusion is drawn that an increase of renin is not responsible for vasoconstriction.

LUISADA.

Lenegre, J., and Maurice, P.: Right Ventricular Pressure in Arterial Hypertension. Arch. d. mal. du coeur **40**:173 (May), 1947.

In twenty-two patients suffering from essential hypertension, intraventricular pressures were recorded from the right ventricular cavity by venous catheterization. Pressures were normal (20 cm. H_2O) in nine, elevated (32 cm. H_2O) in thirteen of the subjects. Hypertension was benign in eight of the nine patients with normal pressure values. Malignant hypertension was present in ten of thirteen examples that demonstrated elevated pressures. It is assumed that in the remaining three patients the elevated ventricular pressure may have constituted an early sign of left ventricular failure.

HECHT.

Lian, C., Welti, H., and Perier, R.: Subtotal Thyroidectomy: Treatment of Mild or Moderate Congestive Failure in Valvular Heart Disease and Normal Thyroid Function. Arch. d. mal. du coeur **40**:212 (May), 1947.

In four patients demonstrating signs of early or moderate congestive failure, subtotal thyroidectomy was well tolerated. The patients were observed for a period of from one to three years. A decrease in dyspnea with improvement in their work performance was noticeable in all. Two of the patients developed signs of hypothyroidism (details are lacking).

HECHT.

Tourniaire, A., Guyot, R., and Rochas, J.: Paroxysmal Tachycardia of Long Duration in a Four-Year-Old Child. Arch. d. mal. du coeur **40**:230 (May), 1947.

The author presents another instance of an auricular paroxysmal tachycardia, apparently arising from the upper portion of the A-V node in a 4-year-old child which had apparently persisted for five months before it was verified. After the diagnosis had been established, frequent paroxysms were observed for a period of ten months. They could not be completely abolished by vagal stimulation but were less frequent on digitalis and quinidine. It is assumed that an increase in the excitability of the A-V node was the underlying cause for the disorder. The child had suffered from measles and chicken pox just before the onset of the paroxysms.

HECHT.

Zabludovich, S.: Pulmonary Atelectasis in Cardiovascular Diseases. Prensa med. argent. **34**:999 (May 30), 1947.

Various pulmonary conditions which occur during heart failure currently are attributed to mechanical disorders resulting from the failure itself. However, many other factors should be considered because enlargement of the heart, dilatation of the vascular pedicle, and exudation of fluid act mechanically on the lungs.

The enlarged heart acts directly on the medial aspects of the lungs and their structures. It acts directly or indirectly on any and all components of the lungs (pleurae, alveoli, bronchi, and vessels). Enlargement of the heart favors pulmonary collapse, atelectasis, and emphysema. These manifestations occur chiefly in the inner aspect of the left lung and around the right auricle. They cause paracardiac x-ray shadows which may simulate mediastinal pleuritis, pleural synechia, or bronchiectasis. Whenever paracardiac atelectasis occurs, it is of parenchymal and not of bronchial

type; it gives a halo of marginal opacity caused by circulatory stasis which later is followed by reabsorption of air. Chronic, progressive atelectasis is accompanied by inflammation and is followed by sclerosis.

Various roentgenologic considerations in the diagnosis of these conditions are given.

LUISADA.

Taquini, H. C., Yodice, A., and Taquini, A. C.: Effects of Gall Bladder Distention on the Normal Heart and the Heart With Experimental Infarction. Rev. Argent. de cardiol. **14**:117 (May-June), 1947.

The effects of acute distention of the normal gall bladder were investigated both in conscious and anesthetized dogs with normal hearts and after coronary occlusion. No changes were detected in the electrocardiogram. The authors conclude that stimulation of a healthy gall bladder does not initiate abnormal reflexes in the heart.

LUISADA.

Mantovani, A., and Lorenzoni, B.: On the Oscillographic Index in Dilatation of the Left Auricle. Folia Cardiologica **6**:51 (June 30), 1947.

The authors studied the amplitude of the oscillographic index in the four limbs of fifty-nine patients with lesions of the mitral valve. The Pachon oscillometer showed that cases with left auricular enlargement present a smaller pulse in the brachial and femoral arteries of the left side. This sign, which is also present in tumors of the posterior mediastinum, is explained as the result of irritation of the sympathetic plexus of the mediastinum by the large left auricle, with resulting vasoconstriction of the vessels on the left side of the body.

LUISADA.

Hopps, H. C., and Lewis, J. H.: Studies on Capillary Permeability as Affected by Anoxemia. Am. J. Path. **23**:829 (Sept.), 1947.

These workers studied the effect of "anoxic" anoxemia on the permeability of capillary endothelium in guinea pigs. To study this subject, they utilized a well-known phenomenon in immunology, namely, the "minimum latent period of passive anaphylaxis," which is the length of time, in hours, that must elapse before an animal becomes susceptible to anaphylactic shock. They reasoned that if anoxic anoxia increases capillary permeability to antibody globulin, the minimum latent period of passive anaphylaxis will be shortened. Guinea pigs sensitized to a specific antiserum (anticrystalline egg albumin-rabbit serum) were subjected to atmospheric pressure similar to that at 30,000 ft. altitude. At this pressure, oxygen concentration is only 6.4 per cent. It was demonstrated that sensitized animals did not develop anaphylactic shock more quickly than control animals.

The authors then showed that a smaller protein molecule, serum albumin, did not pass through capillary endothelium more quickly under the same altered atmospheric pressure. This was proved by the rate of disappearance of a dye from the blood of those animals that received injections of serum albumin combined with Evans blue. The capillary permeability was unchanged in animals under low oxygen tension.

The authors conclude that anoxic anoxia does not alter the permeability of capillary endothelium to protein molecules; that anoxic anoxia thus differs from the local action (for example, on an isolated limb) of stagnation anoxia; and that the classic experiments of Landis on the effect of anoxia on capillary permeability probably deal with effects of increased carbon dioxide rather than decreased oxygen tension.

GOULEY.

Beers, S. D., and de la Chapelle, C. E.: An Unusual Case of Ventricular Tachycardia. Ann. Int. Med. **27**:441 (Sept.), 1947.

A 57-year-old white man was admitted to the hospital with the chief complaint of palpitation of ten hours' duration. There was a history of attacks of palpitation for some twenty years. An electrocardiogram taken about three weeks before the present episode of tachycardia showed a pattern compatible with the Wolff-Parkinson-White syndrome. An electrocardiogram made on

the day of his hospital admission showed the presence of a ventricular tachycardia with a rate of 160 per minute. Various drugs, which included quinidine sulfate, potassium chloride, and magnesium sulfate, were used in an attempt to abolish the paroxysm. There was no immediate success following the exhibition of these drugs. Finally, after twelve days of almost continuous tachycardia, a normal sinus rhythm returned. The possibility that the ventricular tachycardia was initiated by an acute myocardial infarction is raised by the authors, even though there were no definite electrocardiographic changes to substantiate such a diagnosis.

WENDKOS.

O'Neill, J. F.: The Effects on Venous Endothelium of Alterations in Blood Flow Through the Vessels in Vein Walls and the Possible Relation to Thrombosis. Ann. Surg. **126:** 270 (Sept.), 1947.

The author investigated experimentally in dogs the role that alterations in the endothelial coat of veins played in the production of venous thrombosis. First, he devised a technique for studying the normal architecture of the vasa venarum, utilizing staining with benzedine, which, by selectively staining red blood cells, can outline the vessels in which they are contained. Subsequently the specimens were cleared with oil of wintergreen.

When the preparations were examined with a hand lens or a microscope, it was found that the vasa venarum varied in diameter from those of true capillary size with diameters of 10 to 20 μ to those of arteriole or venule proportions with diameters of 60 to 75μ. They were seen in the adventitia but not in the media or intima. No conclusions could be drawn from this observation as to the depth to which the vessels extended, since the findings could have been due to a lack of penetration of the dye beyond the adventitia. The arteriolar vasa venarum were seen entering the venous adventitial coat and then dividing and subdividing to form a rich capillary network which then entered venules. These eventually emerged from the adventitia of the vein wall as venae comites serving the entering arterioles and emptied into veins which ran in the loose perivenous connective tissue. No signs were noted of venous capillaries in the vasa venarum of a vein wall draining directly into the parent lumen.

The effects of destroying the blood supply to a vein and of partial obstruction were studied with regard to changes in the endothelium and the production of clot formation. Staining with silver nitrate was utilized in this problem. It was found that when the venous endothelium was deprived of the blood supply in the vein wall, endothelial damage was produced. Partial obstruction without altering the blood supply was a slightly more frequent cause of intravenous clotting, although it did not produce destruction of endothelium as readily as did a loss of blood supply. The author suggested that both factors might operate in the production of "spontaneous" intravenous clotting.

ABRAMSON.

Wise, A. W., and Miller, W. A.: Subacute Bacterial Endocarditis Due to B. Tularense, Treated by Streptomycin. Illinois M. J. **92:**182 (Sept.), 1947.

The authors present the case of a 31-year-old man admitted to the hospital with a spiking type of temperature ranging between 101° and 103°F. daily. There was a history of a heart lesion since early childhood, probably since birth, which was considered to be a combined pulmonary stenosis and patent intraventricular septal defect. In view of the heart lesion, and definite and specific evidence of embolic phenomena and the febrile course over a period of three to four weeks, a diagnosis of subacute bacterial endocarditis was made, in spite of negative blood cultures. Penicillin was given in doses of 800,000 units daily and continued for twelve days with no reduction in the fever. At this time a definite maculopapular rash broke out over both lower extremities, and a history of a tick bite before entry to the hospital was elicited. Agglutination test for tularemia was positive for *B. tularense* in dilutions as low as 1 to 3,200. It was then felt that tularemia was the basis of the subacute bacterial endocarditis. He was started on streptomycin and was given 800,000 units daily at four-hour intervals by the intramuscular route. After a course of 6,000,000 units in eight days, his temperature dropped to normal and he felt much improved. He was dismissed from the hospital two weeks later with an apparent arrest of the infection.

BELLET.

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ABRAMSON.

Wise, A. W., and Miller, W. A.: Subacute Bacterial Endocarditis Due to B. Tularense, Treated by Streptomycin. Illinois M. J. **92:**182 (Sept.), 1947.

The authors present the case of a 31-year-old man admitted to the hospital with a spiking type of temperature ranging between 101° and 103°F. daily. There was a history of a heart lesion since early childhood, probably since birth, which was considered to be a combined pulmonary stenosis and patent intraventricular septal defect. In view of the heart lesion, and definite and specific evidence of embolic phenomena and the febrile course over a period of three to four weeks, a diagnosis of subacute bacterial endocarditis was made, in spite of negative blood cultures. Penicillin was given in doses of 800,000 units daily and continued for twelve days with no reduction in the fever. At this time a definite maculopapular rash broke out over both lower extremities, and a history of a tick bite before entry to the hospital was elicited. Agglutination test for tularemia was positive for *B. tularense* in dilutions as low as 1 to 3,200. It was then felt that tularemia was the basis of the subacute bacterial endocarditis. He was started on streptomycin and was given 800,000 units daily at four-hour intervals by the intramuscular route. After a course of 6,000,000 units in eight days, his temperature dropped to normal and he felt much improved. He was dismissed from the hospital two weeks later with an apparent arrest of the infection.

BELLET.

Thorsen, G.: Dicoumarol Poisoning With Relapse. Lancet **2**:420 (Sept. 20), 1947.

The author reports a case of Dicumarol poisoning which was apparently successfully treated with blood transfusions and vitamin K but in which a relapse occurred three and one-half months after the Dicumarol had been stopped.

A 41-year-old woman with tetany for whom dihydrotachysterol was prescribed was given Dicumarol. By mistake she received 0.50 Gm. daily in the first week and 0.75 Gm. daily for the next two weeks, a total of 14 Gm. in three weeks. The day before admission to the hospital she developed severe epigastric pain, vomited blood stained mucus, and was thought to have a perforated duodenal ulcer. On admission, her general condition was poor, and she showed most of the signs seen in experimental Dicumarol poisoning in animals. For nearly three weeks she continued to bleed at intervals from the gums, nose, gastrointestinal and urinary tracts, and uterus, and into the peritoneal cavity. Sometimes the bleeding was profuse but there were no cutaneous or subcutaneous petechial hemorrhages. Repeated transfusions of fresh blood were given during the first seven days. In addition, 200 to 400 mg. of sodium 2-methyl-1, 4 naphthahydroquinone diphosphate were given by month daily for fifteen days, supplemented during the last seven days with 10 to 30 mg. intravenously. The patient gradually recovered and all symptoms disappeared. Nine weeks later the patient returned to the hospital. For three or four weeks she had complained of fatigue, apathy, decreasing power of concentration, and loss of memory. In the last two weeks there had been bleeding from the nose, gums, and vagina. Treatment during the first week consisted of blood transfusions only. Bleeding continued throughout the week with a short cessation immediately following the transfusions. Treatment with vitamin K was begun, the blood transfusions being continued for four days. After the start of vitamin K therapy the bleeding soon ceased, and three months after the end of all treatment, the blood findings were still normal.

The suspicion that the patient had taken Dicumarol in the interval between the two hospital admissions was not borne out and the second episode of bleeding therefore appeared to be a late result of previous Dicumarol medication.

BELLET.

Watkins, E., Jr.: Circulatory Changes Produced by Clamping of the Thoracic Aorta. Surgery **22**:530 (Sept.), 1947.

Watkins concludes from his experiments on dogs that Gross' analysis of the cause of death in his first patient operated upon for coarctation of the aorta is correct. Gross believed that the child died from cardiac failure following sudden release of the aortic clamps upon the completion of the end-to-end suture anastomosis. In turn, cardiac failure was due to inadequate venous return from the splanchnic area where a large volume of blood pooled following the sudden opening of an enormous vascular bed.

In ten acute experiments on dogs, Watkins showed that clamping of the thoracic aorta just beyond the left subclavian artery was associated with the following circulatory changes: (1) prompt and significant rise in the pressure in the carotid artery; (2) a similar rise in the pressure in the superior vena cava; (3) an abrupt fall in the pressure in the femoral artery; (4) a decrease in splanchnic volume (small intestine); and (5) an increase in pulse rate. After sudden removal of the clamp the following changes were noted: (1) marked and sudden fall in the carotid artery pressure which gradually returned to the level which existed before clamping; (2) slow rise to normal of the femoral pulse pressure; (3) a slow fall in the superior vena cava pressure; (4) gradual increase in splanchnic volume to a much greater volume than before the clamping; and (5) a significant tachycardia, particularly noted when cyclopropane was employed as the anesthetic agent instead of intravenous Nembutal. These changes are explained by the poor venous return associated with pooling of blood in the splanchnic area which is due to vasodilatation resulting from the collection of metabolites in this area.

In contrast, Gross' suggestions of slowly releasing the aortic clamps and placing the patient in the Trendelenburg position were well corroborated by one experiment in which these precautionary procedures were carried out; the splanchnic volume did not increase above normal and the carotid artery pressure returned gradually to normal.

LORD.

Lowell, A., Cournand, A. and Richards, D. W., Jr.: Changes in Plasma Volume and Mean Arterial Pressure After the Intravenous Injection of Concentrated Human Serum Albumin in Thirty-Eight Patients With Oligemia and Hypotension. Surgery **22**:443 (Sept.), 1947.

The authors studied the plasma volume, hematocrit, serum protein concentration, and mean arterial blood pressure before and after the injection of concentrated human serum albumin. From these data they were able to calculate total circulating protein, the total circulating albumin, the plasma volume increase per gram of albumin injected, and the plasma volume increase per gram of albumin retained.

The amount of human serum albumin injected varied between 24 and 64 Gm. (25 per cent solution). The authors observed that the average increase in plasma volume for twenty cases studied was 520 c.c. after an average injection of 46 grams. The average increase in plasma volume per gram of albumin injected was 12 cubic centimeters. In patients with continuous blood or plasma loss, the average increase was only 7 cubic centimeters. When an infusion of 400 c.c. of saline was administered with the albumin, then the average increase in plasma volume was 15 c.c. per gram of albumin.

The average injection of 46 Gm. of concentrated human serum albumin solution alone produced a rise in the mean arterial blood pressure of 17 mm. of mercury. The authors point out that, in general, the blood pressure did not return to normal and believe this finding is due to a decrease in the viscosity of the blood which is a resultant of the increase in the plasma volume.

Studies of a salt-poor albumin solution showed no significant difference in response when compared with the standard salt-containing concentrated human albumin solution.

LORD.

Crafoord, C., Ejrup, B., and Gladnikoff, H.: Coarctation of the Aorta. Thorax **2**:121 (Sept.), 1947.

In experimental studies on dogs, Crafoord (1939) demonstrated that the flow of blood to all organs could remain suspended for as long as twenty to twenty-five minutes without any subsequent sign of organic damage, provided an adequate flow to the brain was secured. This circulation to the brain was maintained by creating anastomoses between the carotid artery and jugular vein on one side in the animal under operation with the corresponding vessels in a dog of the same size lying beside it.

On the basis of this observation, Crafoord took the risk, in certain patients with a patent ductus arteriosus, of placing clamp forceps on the aorta above and below the point of entry of the duct into this artery and of keeping them attached during the time necessary to divide the duct and suture the aorta; in one of the patients this part of the operation took no less than twenty-seven minutes to perform. No noticeable disturbances were subsequently observed in the patient's internal organs. Crafoord considered that in patients with congenital isthmic stenosis who already possessed a well-developed and satisfactorily functioning collateral arterial system, he could venture to keep the aorta closed at a point immediately peripheral to the left subclavian artery for a period considerably longer than twenty-seven minutes without causing danger to the patient through cutting off the blood flow to organs in the part of the body supplied with arterial blood from arteries peripheral to the aortic stenosis.

In fifteen patients with coarctation, one death occurred in the last eight; this was due to a false aneurysm caused by insufficiency of the aortic suture line.

Three principal developmental disturbances may be associated with the adult form of coarctation of the aortic isthmus. These include bifid aortic cusps, which has an incidence of 25 per cent, hypoplasia of the aortic wall which was found in 10 per cent of the series, isolated cases, in which the points of origin of the great vessels leaving the aortic arch are abnormally situated, and also cases of patent ductus arteriosus. The average life span of patients with coarctation seems to be low; about 25 per cent of all patients die before they reach the age of 20 years, one-half of all patients do not survive beyond the age of 40 years, and 90 per cent die before the age of 50 years. Thus, only 10 per cent of all patients live 50 years or longer. The causes of death, in order of frequency, are congestive heart failure, sudden death due to rupture of the aorta or the heart, cerebral hemorrhage, and bacterial endocarditis.

Operation resulted in great changes in the pulse quality in the upper and lower limbs and in the collateral vessels. The hypertensive pulse in the arms became normal; the pulse in the legs, impalpable before operation, became normal after operation, and the pulse in the collaterals, palpable before operation, became impalpable in patients observed for a longer period of time. Hypertension in the upper limbs and hypotension in the lower limbs were present in all cases before operation and returned to normal after operation.

BELLET.

Master, A. M., and Auerbach., O.: A Case of Acute Myocardial Infarction Without Acute Coronary Artery Occlusion (Acute Coronary Insufficiency Without Acute Occlusion). J. Mt. Sinai Hosp. **14**:491 (Sept.-Oct.), 1947.

The authors give a short history of a patient who suffered from acute myocardial infarction without acute coronary artery occlusion in whom the diagnosis was made ante mortem.

A man, 37 years of age, was admitted to the hospital with the diagnosis of coronary heart disease. The electrocardiogram showed a flat T_2 and inverted T_3 and occasional premature ventricular beats. The patient began to improve and the electrocardiogram returned to normal. News of his father's sudden death from acute coronary artery occlusion resulted in a return of the precordial pain which became quite severe. He went into shock and died the next morning. The electrocardiogram the day before death showed deep depressions of the RS-T segments in Leads I, II, and IV with semi-inverted T waves.

At autopsy, there was found congestion of the lungs, liver, and other viscera due to heart failure. The heart showed necrosis which even grossly could be seen to involve chiefly the subendocardial layer. Microscopically, there were innumerable areas of necrosis and fibrosis in the subendocardial layer of the muscle. Both coronary arteries and their branches showed advanced sclerosis, but cross sections of these vessels disclosed no acute occlusion. The type of acute coronary artery disease under discussion, acute myocardial infarction without acute coronary artery occlusion, or simply "acute coronary artery insufficiency," is intermediate between the ordinary bout of angina pectoris and the complete acute closure of a coronary vessel.

BELLET.

Sirota, J. H., Gerber, I. E., and Baehr, G.: Chemotherapy of Subacute Enterococcus Endocarditis. J. Mt. Sinai Hosp. **14**:604 (Sept.-Oct.), 1947.

The authors report that among a group of forty patients treated for subacute bacterial endocarditis since penicillin first became available, four were caused by the enterococcus. One of these was treated with penicillin alone, two with massive sulfonamide therapy and penicillin, and one with streptomycin alone.

Case 1 is the first reported cure of enterococcus endocarditis by penicillin. The organism was only five times as resistant to penicillin as the standard Staphylococcus H. Two hundred thousand units of penicillin per day by constant intravenous drip produced blood levels varying between 0.2 and 0.8 units per cubic centimeter. The second course which consisted of 500,000 units of penicillin daily for one month, raised the blood levels to 0.8 to 1.6 units per cubic centimeter.

In Case 2, the patient required a concentration of 3 units of penicillin per cubic centimeter in vitro for bactericidal effect. The last course of penicillin consisted of 10,000,000 units per day for thirty-five days. With this dosage, blood levels ranging from 5.0 to 107 units per cubic centimeter were obtained, that is, levels from 1.7 to 35 times the concentration considered necessary to inhibit growth in vitro. Massive administration of sulfonamide accomplished little, except to produce transient azotemia and perhaps some prolongation of the subsequent therapeutic penicillin blood levels. After completion of the various courses of therapy, the resistance of the organism had increased somewhat.

In Case 3, the patient died during his eleventh week in the hospital. The organism was a fairly sensitive enterococcus, being only twenty-five times as resistant as the standard organism to penicillin. Six hundred thousand units of penicillin per day for four weeks succeeded in sterilizing the blood stream, but not the vegetations.

In Case 4, the initial treatment with streptomycin was begun a short time after the organism had implanted itself upon the heart valves. A five-day intensive course, using a total of 20 Gm. of streptomycin, was sufficient to cause complete clinical remission for a period of three months, in spite of a relatively resistant organism. The authors believe this duplicates their experience with penicillin-treated cases in which they found that smaller doses over a longer period of time were more efficacious in producing permanent cures than massive doses over a short period of time. They believe that a permanent cure would have been effected had the initial streptomycin course of 4.0 Gm. per day been continued for four to five weeks. This patient was readmitted to the hospital three months after the apparent arrest of the infection. At the time, however, a total of 41 Gm. of streptomycin given over a period of one month had no effect on the clinical course. The blood cultures were persistently positive for enterococcus, the resistance being ten times that of the standard organism. At the time of this report this patient was still febrile.

BELLET.

Murray, G.: The Pathophysiology of the Cause of Death From Coronary Thrombosis. Ann. Surg. **126:**523 (Oct.), 1947.

Murray exposed the hearts in a series of dogs and ligated the anterior descending branch of the left coronary artery. Observations were made of the area of myocardium supplied by that artery, the cardiac output, the blood pressure, the electrocardiogram, and pulse rate. In some experiments the ligature was removed after a few seconds.

The author then carried out in twenty-five dogs a series of resections of the areas in which an infarct developed and obtained excellent healing and good recovery in each animal. The heart functioned well and the animals remained well for from one to two years.

Murray discusses the possible clinical application of this procedure in coronary thrombosis as it is seen in man.

LORD.

Heinbecker, P.: Factors Limiting Surgery for Essential Hypertension. Ann. Surg. **126:** 535 (Oct.), 1947.

As a result of observations made on patients with Cushing's syndrome and studies made on experimental animals, Heinbecker presents an hypothesis of the underlying basis of essential hypertension. "It is postulated that functional influences in the central nervous system, particularly in the frontal lobes of the cerebral cortex, normally may depress the hypothalamic nuclei which control the secretion of the neural hypophysis . . . On depression of the functional activity of these nuclei there results a diminution in the secretion of the neural hypophysis. This, on the basis of the experimental evidence presented, can be assumed to result in a stimulation of the eosinophil cells of the glandular hypophysis, and these in turn stimulate the adrenal cortex to greater activity. The combined influence of the anterior pituitary hormone and of the adrenal cortical hormone is to effect a constriction of the efferent glomerular arterioles of the kidney and a release of renin. The combined action of all three hormones here, as in Cushing's syndrome, is held responsible for the arteriolar narrowing and the development of diastolic hypertension."

The author believes that there must be an underlying constitutional susceptibility of the smooth muscles of the blood vessels to the vasoconstricting action of the three humoral agents in order that diastolic hypertension may develop.

The only role sympathectomy can play in relieving diastolic hypertension, according to this hypothesis, is the denervation of the adrenal glands, and hence, a lowering of the output of epinephrine which in turn exerts an unfavorable influence on the excitability of the central nervous system for influences which normally lead to a depression of the hypothalamus.

The extent of the sympathectomy necessary to accomplish denervation of the adrenals is limited to bilateral removal of the first and second lumbar ganglia and sectioning of the splanchnic nerves prior to their junction with the celiac ganglia. More extensive sympathectomies, in the author's opinion, serve no useful purpose.

LORD.

Costero, I., and de Buen, S.: Descending Myocarditis Subsequent to Luetic Mesaortitis. Arch. Inst. Cardio. de Mexico **17**:605, (Oct. 31), 1947.

In addition to the better known type of diffuse, interstitial, hematogenous myocarditis, another type may be found. It spreads by continuity from the aorta and is common in patients with syphilitic aortitis. The best technique for studying this type of myocarditis is described. The myocardial lesion originates from inflammatory foci in the media and spreads first to the areas adjacent to the sinus of Valsalva. Endoangiitis obliterans, perivascular infiltration with lymphocytes and plasma cells, and intimal thickening at the origin of the coronary arteries frequently are found. The inflammatory infiltrates of the adventitia in the supracoronary part of the aorta can spread easily to the pericardium. This descending myocarditis exceptionally has a gummatous form; in such cases an A-V block is common.

Different changes of the myocardium, of degenerative, inflammatory, or fibrotic type, probably are caused by coronary ostial stenosis or are the result of coronary insufficiency.

LUISADA.

Aceves, S., and Carral, R.: Diagnosis of Tricuspid Lesions. Arch. Cardiol. de Mexico **17**:701 (Oct. 31), 1947.

The authors analyze the signs and symptoms of fifty cases with severe tricuspid lesions recognized at autopsy. These cases represent 33.3 per cent of all rheumatic cases autopsied at the National Institute of Cardiology.

The most important findings were: (1) In all cases, the tricuspid lesion was associated with a mitral lesion; in many, an aortic lesion also was present; exceptionally, all valves were involved. (2) Whenever the lesion was diagnosed during life, a systolic murmur with special characteristics was present over the xiphoid area. This murmur increased in intensity during deep inspiration and in the following apnea, while the mitral murmur had a different behavior. (3) Enlargement and increased firmness of the liver were constant. (4) Cyanosis was present in 56 per cent of the cases, distention of the jugular veins in 86 per cent, systolic jugular pulse in 36 per cent, and hepatic pulse in 42 per cent. (5) Right deviation of the electrical axis of P of more than 60 per cent and delay of 0.04 second or more of the intrinsic deflection in Leads V_1 and V_2 were found in over one-half of the cases. (6) Various x-ray signs were observed: enlargement of the right auricle or ventricle; pulsation of aortic type without lesion of the aortic valve; double contour of the right auricular salient; dilatation of the superior cava; and triangular or globular shape of the heart.

LUISADA.

Boynton, R. E., and Todd, R. L.: Blood Pressure Readings of 75,258 University Students. Arch. Int. Med. **80**:454 (Oct.), 1947.

The results of blood pressure determinations on 75,258 persons examined at a Student Health Service are analyzed. Most of these were under the age of 26 years, and men outnumbered women by about three to two. The mean systolic pressure for men was 122 mm. and for women, 111 mm. Hg, while the mean diastolic was 74.5 mm. Hg for men and 69.7 mm. Hg for women. The mean systolic pressure of women showed a tendency to rise with age, a trend not seen in men. The tendency for the diastolic to rise with age was present in both sexes. A greater percentage of women than men had systolic pressures below 109 mm. Hg, whereas systolic pressures above 120 mm. Hg occurred more frequently in men.

BERNSTEIN.

Stearns, S., Schlesinger, M. J., and Rudy, A.: Incidence and Clinical Significance of Coronary Artery Disease in Diabetes Mellitus. Arch. Int. Med. **80**:463 (Oct.), 1947.

This paper emphasizes the fact that although advanced coronary artery disease is generally accepted as a frequent complication of diabetes, the high incidence has not been fully appreciated. The most important factor in the underestimation of the severity of coronary heart disease in diabetic patients is the imperfection of post-mortem examination of the arteries. The injection

plus dissection technique combined with the microscopic examination of the myocardium make it possible to establish rational criteria for estimating the functional significance of the coronary artery disease in a given heart. The present study demonstrated that at the time of death functionally significant coronary heart disease was present in three-fourths of the diabetic patients. One-third of these died of acute coronary heart disease, and one-fourth of the group had had angina pectoris. Among diabetic women over the age of 40 years, the incidence of significant coronary arteriosclerosis, of angina pectoris, and of death due to coronary artery disease is as great as among diabetic men (in sharp distinction to the sex difference in these respects in the nondiabetic population). Angina pectoris, deaths due to acute coronary disease, and congestive heart failure are all more common when hypertension is present in the diabetic. The severity of the coronary arteriosclerosis is correlated with the duration and not with the severity of the diabetes. Any diabetic man or woman over the age of 40 years can be assumed to have advanced coronary artery disease even in the absence of symptoms, particularly if hypertension is present, or if diabetes is of more than ten years' duration.

BERNSTEIN.

Tucker, H., and Farmer, T. W.: Penicillin in Cardiovascular Syphilis. Arch. Int. Med. **80**:322 (Sept.), 1947.

Thirty patients with late cardiovascular syphilis were treated by the intramuscular route with sodium penicillin in aqueous solution in total dosages ranging from 2,000,000 to 15,000,000 Oxford units. Two of the patients had anginal attacks during treatment which were comparable, however, to attacks noted prior to treatment. Only five had febrile reactions within the first sixteen hours. There were no significant differences in the incidence of febrile reactions or cardiovascular symptoms in patients receiving initial doses of 500 to 3,000 Oxford units as compared with those given large initial doses (25,000 to 100,000 units) of penicillin. It is the opinion of the authors that the dangers of untoward reactions may have been unduly emphasized, but more work must be done in patients with cardiovascular syphilis before final conclusions are justified.

BERNSTEIN.

Altschule, M. D., Freedberg, A. S., and McManus, M. J.: Effects on the Cardiovascular System of Fluids Administered Intravenously in Man. Arch. Int. Med. **80**:491 (Oct.), 1947.

During intravenous infusions of 1,800 c.c. of normal saline or 5 per cent glucose in isotonic saline at a rate of 60 to 85 c.c. per minute, capillary microscopy reveals a progressive dilation of the small blood vessels of the fingernail fold with a greatly accelerated blood flow. These changes began shortly after the start of the infusion, and within twenty to forty minutes after the termination of the infusion, most or all of the changes disappeared, suggesting a return of circulating volume to preinfusion levels.

Cutaneous lymphatic flow was likewise greatly increased apparently as a consequence of the loss of fluid from the circulation into the skin. Accumulation of fluid consequent to increased filtration from the circulation is greatest in the skin and pulmonary parenchyma. Large volumes of fluid may exist in the skin without causing symptoms or being detectable. In the case of the lungs, however, the accumulation of excessive fluid may precipitate respiratory signs and symptoms. Accordingly, it is not surprising in patients in whom pulmonary edema is latent because of the presence of cardiac or pulmonary disease, uremia, etc., that overt manifestations of that disorder may be caused during or after the intravenous infusions of a solution of electrolytes.

BERNSTEIN.

Reals, W. J., Russum, B. C., and Walsh, E. M.: Primary Mesothelioma of the Pericardium. Arch. Path. **44**:380 (Oct.), 1947.

The authors report an incidence of the rare primary mesothelioma of the pericardium, of which twenty-two cases have been previously reported. The patient was a 58-year-old white man, complaining of cough and chest pain on exertion for six weeks following an upper respiratory

infection. He coughed up bright red blood on several occasions during this time. Dyspnea and hemoptysis became worse, casting doubt on the primary diagnosis of pneumonia. There was no weight loss, and the past history was irrelevant. There was no cyanosis. The cardiac apex was located in the normal site, and the heart action was regular at a rate of 86 per minute. No friction rub and no murmurs were heard. There was a marked anemia and a moderate leucocytosis. X-ray examination showed fluid in the right pleural cavity, and after withdrawal of 500 c.c., the right upper lobe was found to be atelectatic. The right side of the diaphragm was elevated. The thoracic fluid was sterile. Marked dyspnea preceded the patient's death.

Autopsy showed a distended pericardial sac containing 1,000 c.c. of bloody fluid. The surface of the left ventricle and the entire conus of the heart were studded with hard, white tumor masses up to 3.0 cm. in diameter. Similar masses were found on the internal aspect of the parietal pericardium and over the great vessels within the cavity. The coronary arteries were patent and uninvolved. The myocardium showed nothing of note. The adjacent pleura of the right lung was similarly studded, and some of these small masses pierced the pericardial sac and formed a large mass at the hilus. The bronchi were carefully examined but no tumor growth was found, although the right upper bronchus was compressed. The left lung contained many scattered nodules. Microscopic examination of sections of the tumor revealed a mesotheliomatous type of growth with some slight suggestion of whorl formation. Mitoses were common. The hilar nodes contained areas of similar growth. Likewise, on the adjacent pleura, the same growth was noted histologically.

GOULEY.

Hirsch, E. F., and Orme, J. F.: Sensory Nerves of the Human Heart. Arch. Path. 44:325 (Oct.), 1947.

The authors were interested in the existence, location, and number of the finer nerve trunks, the individual nerve fibers, and the nerve endings within the heart. Most of the previous work on this subject was done on lower animals. The writers studied blocks of tissue from the hearts of one infant and three adults; all of the blocks of tissue from adults were from the left ventricle along the anterior descending branch of the left coronary artery. Serial sections were taken beginning at a level 2.5 cm. from the origin of this vessel. Various stains were employed, including those for myelin.

It was found that the branches of this important vessel were accompanied by nerve trunks of varying sizes, these trunks accompanying the branch vessels through the myocardium to the subendocardial areas. Often more than one nerve trunk accompanied the artery, and generally they were situated within the compact tissue of the adventitia. The size of these nerve trunks gradually decreased toward the endocardium. Branches of the myelinated fibers soon lost the myelin upon breaking up into their final distribution within the adventitia of the vessel. No nerve ganglion cells were found in the epicardial tissues of the ventricle (at the base of the heart), but they were observed within the auricle.

The presence of myelinated nerve fibers in the heart in areas not requiring motor function indicated that these are afferent fibers. The authors believe that the myelinated nerve structures which they describe, accompanying the anterior descending coronary artery, represent the sensory system that transmits painful stimuli. They are able to find some terminal branches, at intervals, that extended into the smooth muscle of the media.

The changes of arteriosclerosis usually occur in the first portion of the coronary arteries at the base of the heart where the nerve supply is greatest. The distribution of these myelinated nerves in the fibrous tissue along the coronary artery, and the penetration of their terminal branches into the walls of the vessels suggest that the stimuli for pain develop in these structures. The authors believe that acute pathologic changes involving the arterial walls, with or without dissection, are more important stimuli of pain than anoxemia of the heart muscle itself. They emphasize the fact that myelinated fibers are afferent and associated with sensory function, and that in the heart they closely follow the coronary wall structure.

GOULEY.

Blumenthal, L. S.: Pathologic Significance of the Ductus Arteriosus. Arch. Path. 44:372 (Oct.), 1947.

The author studied histologically the degenerative changes that precede the closure of the ductus arteriosus, from the special viewpoint of its correlation with arteriosclerosis in general pathology. Sections were from a series of 175 specimens obtained from fetuses and from persons of various ages. Various stains were employed to bring out changes in the elastic, muscular, and connective tissues.

Sections from fetuses and from normal infants up to the age of twelve days showed little difference except that the media in the latter was more cellular, the lumen reduced in diameter, and the general appearance of a more active and contracting media, therefore, was presented. Degenerative changes made their first appearance in infants ranging from twelve days to two months of age. There seemed to be an ischemic appearance of the wall, fibrosis made its first appearance in the media, and the lumen of the ductus was compressed to a slit. Gradually the muscle cells had become paler, and fibrous tissue had infiltrated into the media. Elastic tissue increased, while smooth muscle tissue decreased. Actual necrosis was rare in very young infants, but gradually increased, together with calcium deposition, in infants ranging up to one year of age. The narrowed lumen continued to contain many red blood cells, and in some cases an attempt at recanalization was apparent. Fibrosis gradually increased.

At the age of one year or over, fibrosis was marked; it had replaced smooth muscle in the outer part of the media. Small clusters of smooth muscle cells remained, in conjunction with persistent capillary processes. When the latter disappeared, ischemic fibrosis became dominant. The internal elastic lamina remained intact, even in the older specimens, and a degenerative type of elastosis appeared with advancing years. In elderly people, cartilage developed at times in the scarred remnants of the ductus arteriosus.

A comparison of the muscular structure of the ductus in the fetal and in the postnatal states indicates that it is an active muscular structure, confirming physiologic studies showing active contraction to be present as a part of its function. But as early as twelve days after birth, and continuing thereafter, there is a progressive loss of muscular structure.

The author works on the premise that the ischemic degeneration here observed, and noted in other organs after cessation of function (uterine arteries in the puerperium), is similar to the fundamental changes in arteriosclerosis throughout the body; all are dependent on anoxemia.

GOULEY.

Oettle, A. G.: Sudden Death After Intravenous Injection of a Mercurial Diuretic ("Neptal"). Brit. M. J. 530 (Oct. 4), 1947.

The author presents the case of a patient, 31 years of age, who was admitted to the hospital complaining of swelling of the legs, reduction in urinary output, dull backache, and dimness of vision. She had suffered from frequent sore throats for many years and four and one-half years prior to admission had had rheumatoid arthritis which responded poorly to treatment with gold injections.

The patient was confined to bed and given a diet high in protein and low in salt, with iron tonics. On the fifth day after admission a mercurial diuretic (Neptal) was injected intramuscularly. Within thirty-two days she received a total of 24.5 ml. of this preparation. Because the intramuscular injections were painful, the intravenous route was adopted. After the fourth intravenous injection, she complained of giddiness and became pale for a few seconds shortly after the needle had been withdrawn. The next day she complained of a sore throat and generalized joint pains. Two days later 2.0 ml. of Neptal was injected into the right median antecubital vein. Immediately on withdrawal of the needle the patient turned pale and became unconscious. Cyanosis rapidly supervened and the breathing, which became gasping, ceased about two minutes after the onset of the attack. On clinical grounds, the authors believe that the injection of Nepal brought about a sudden cessation of the heart beat, presumably by ventricular fibrillation.

BELLET.

Deterling, R. A., Jr., Essex, H. E., and Waugh, J. M.: Experimental Studies of Arteriovenous Fistula With Regard to the Development of Collateral Circulation. Proc. Staff Meet., Mayo Clin. **22**:495 (Oct. 29), 1947.

A series of nineteen adult dogs was observed over a period of seven to ten months following the production of a femoral arteriovenous fistula 1.5 to 3 cm. in length. Studies of blood volume showed an average increase of 30.87 per cent, and measurements of the cardiac silhouette on roentgenograms showed an average increase of cardiac area of 32.56 per cent. When the animals were finally sacrificed after the observations on the cutaneous temperature had been completed, the vascular tree was injected with a radiopaque mass. It was readily demonstrated that in the injected animals in which the fistula was patent, there developed a tortuous dilated "Medusa's head" network of vessels which has on occasion been referred to in the literature as the "collateral" circulation. Of great significance is the fact that the majority of these vessels had been previously venous channels, but after the formation of a fistula they carried mixed arteriovenous blood as a result of the intervascular communication.

The anastomosis was excised in several animals and only the arterial bed was injected via the aorta. In some of the animals there was only slight evidence of an arterial response even though the fistulas had existed for more than six months.

Before the injection studies were carried out, this group of nineteen animals was studied during the seven-month period following the formation of a femoral arteriovenous fistula. Cutaneous temperatures of the paws were measured. Immediately after production of the fistula, the cutaneous temperature of the fistulous limb fell almost to air temperature. After twelve to twenty-four hours, there was a slight but rapid rise, indicating some release of vasospasm. Thereafter, for about ten days there was a gradual increase of temperature until a level about 1.5 to 2° C. below that of the control side was reached. Subsequently, on exposure to a room temperature of 10° C. for thirty minutes, the temperature of the control limb fell to a level slightly lower than that of the fistulous limb. After seven months, quadruple ligation and excision of the patent fistula were performed on certain animals of the group. The accompanying rise in toe temperatures in the fistulous leg represents redistribution of the arterial blood volume through the distal capillary beds on closure of the fistula.

After the arteriovenous fistula had been functioning for more than six months, seven animals were selected for lumbar sympathectomy. An interesting and constant finding was a lag in response of the fistulous leg to anesthesia. In four animals bilateral extirpation of the lumbar sympathetic ganglia and chain in one stage was performed so as to have a control response to sympathectomy. In the remaining three dogs, sympathectomy was performed on the side with the fistula only. In the former group there was an immediate and sustained postoperative rise of about 4.5° C. in both limbs, with the previous temperature differential between the fistulous leg and the control leg maintained. In the unilateral sympathectomized group, while the elevation of temperature of the sympathectomized side was sustained thereafter, that of the control side fell to the preoperative level after the effects of the ether anesthesia were dissipated. To test the efficacy of the sympathectomy in this group, these animals were placed in the cool room for thirty minutes. The normal side responded with marked vasoconstriction and a drop of cutaneous temperature to about 23° centigrade. Following quadruple ligation and excision of the fistula in certain of these animals, there was a rise of temperature in the sympathectomized limb as a result of the redistributed distal arterial flow.

BELLET.

Shumacker, H. B., Jr.: Sympathectomy as an Adjuvant in the Operative Treatment of Aneurysms and Arteriovenous Fistulas, I. Sympathectomy Performed Before or at Time of Operation. Surgery **22**:571 (Oct.), 1947.

The author carried out seventy-nine sympathectomies, twenty-four dorsal and fifty-five lumbar, either before or at the time of the operative procedure for arterial aneurysm or arteriovenous fistula. There were, in the entire group, eighty-four patients with arterial aneurysms, of whom 34.5 per cent were sympathectomized, and 206 patients with arteriovenous fistulas, of whom 22.6 per cent were sympathectomized. No deaths or serious complications followed the seventy-nine sympathectomies.

As a result of his extensive experience, the author believes that sympathectomy is valuable in improving the collateral circulation in the vast majority of patients, and hence is a worthwhile adjunct in the successful management of these vascular lesions. However, sympathectomy is no guarantee against the possible development of ischemic changes in the extremity; gangrene of part of the foot ensued in one case.

The indications for sympathectomy are the following:

(1) Evidence of an inadequate collateral circulation when the main artery proximal to the lesion is occluded and the reactive hyperemia test of Matas is employed. (2) Associated injury to the contiguous nerves. The desirability of early repair of damaged nerves precludes the waiting period desirable for nature to build a good collateral circulation, and hence, sympathectomy may be employed early to improve and hasten the collateral circulation. (3) In some locations it is impossible to carry out the Matas test, and sympathectomy should be performed as a safety measure. Occasionally under these circumstances it may prove to have been unnecessary. (4) When vasospasm is an associated factor, then sympathectomy is most important. (5) Sensitivity to cold is lessened by sympathectomy, although some degree of sensitivity may remain in some patients. (6) When ischemic lesions are already present, then sympathectomy is indicated, as operation subsequently on the aneurysm or fistula is likely to embarrass further the collateral circulation. (7) When causalgia is present, then sympathectomy may have a worth-while effect.

Shumacker points out that lumbar sympathectomy has no beneficial effect on limited exercise tolerance following a surgical procedure for arterial aneurysm and arteriovenous fistulas of the femoral and popliteal arteries. Exercise tolerance is unlimited only in those cases where continuity of flow in the main artery was preserved either by suture of the orifice of the fistula or by vein graft.

LORD.

Shumacker, H. B., Jr.: Sympathectomy as an Adjuvant in the Operative Treatment of Aneurysms and Arteriovenous Fistulas, II. Sympathectomy Performed After Operation. Surgery **22**:597 (Oct.), 1947.

The author analyzed the results of sympathectomy performed in thirty-eight patients subsequent to earlier operations carried out for the cure of arterial aneurysms and arteriovenous fistulas. The results ranged from excellent to fair in all cases; only two patients developed gangrene, one of the foot and the other of the thumb. The chief indications for sympathectomy were: "1. distressing sensitivity of the limb to cold; 2. associated severe peripheral nerve damage in limbs in which the circulation was definitely impaired; 3. persistent edema; 4. ischemic nerve paralysis; 5. causalgia relieved temporarily but not cured by sympathectic blocks; 6. obviously impending gangrene; 7. evidence of sympathectic overactivity, with or without poor collateral circulation, in a limb in which another arteriovenous fistula required excision."

Shumacker favors surgical sympathectomy over denervation by injections of alcohol because of the danger of an associated neuritis when the latter is used. Again, he points out that sympathectomy is of little aid in relieving poor exercise tolerance resulting from an operation on arterial aneurysms and arteriovenous fistulas in which the main artery has been ligated.

In patients with persistent and significant degrees of edema, sympathetic blocks may show little benefit, whereas sympathectomy is usually most successful.

LORD.

Stewart, J. D., Kennedy, P. A., and Hale, H. W., Jr.: A Study of Systolic Blood Pressure and Pulse Rate in Traumatic Shock. Surg., Gynec., & Obst. **85**:453 (Oct.), 1947.

The authors analyzed the systolic blood pressure and pulse rates of 204 severely wounded soldiers at the time of their admission to forward field hospitals and at the beginning and end of the operative procedures. They concluded that: (1) Marked lowering of the systolic blood pressure and a marked elevation in the pulse rate were observed more frequently in the group with fatal outcome than in those who recovered. However, some patients with significant changes from normal in these two vital signs recovered, and others with less advanced changes died. (2) The essential disturbances of a state of traumatic shock, such as decreased cardiac output, di-

minished peripheral blood flow, and tissue anoxia are not reflected accurately by the systolic blood pressure and pulse rate. In fact, these two vital signs "should be considered as representing the momentary effect of varied and compounded physiological reactions."

LORD.

Leriche, R.: Arteriectomy in Obliterative Arteritis of the Aged, Based on 144 Observations. Union méd. du Canada, 76:1162 (Oct.), 1947.

The author considers arteriectomy the treatment of choice for senile arterial obliteration. Summarizing his experience and with illustrative case reports, he points out that the operation should be performed early in the course of the disease before the development of gangrene. Unfavorable cases are those exhibiting marked cyanosis and edema of the lower legs, but even these are sometimes greatly benefitted. The most favorable cases are those presenting intermittent claudication, nocturnal pain, vasomotor disorders, and dependent erythema. The most refractory symptom is intermittent claudication which in some cases does not disappear until as long as a year after operation.

Because of the war, no follow-up was possible in many of the author's 144 cases; but of those under continued observation, favorable results with stabilization of the disease occurred in 45 to 50 per cent. Failure was caused predominantly by too late intervention when the patients were no longer operable. Of this group, twenty-seven cases required secondary amputation. There have been nine deaths.

Arteriectomy should be as extensive as possible, and for the superficial femoral artery should include 15 to 25 cm. of the vessel. It should generally be made under local anesthesia. Lumbar ganglionectomy, in addition to arteriectomy, increases the chances of success.

LAPLACE.

Underdahl, L. O., and Smith, H. L.: Coronary Artery Disease in Women Under the Age of Forty. Proc. Staff Meet., Mayo Clin. 22:479 (Oct. 15), 1947.

The authors studied the records of 95,000 women under the age of 40 years who were seen at the Mayo Clinic during the eleven-year period, 1935 through 1945, and found a total of twenty-seven patients in whom there was no reasonable doubt of the diagnosis of coronary disease. This gives a ratio of about one case of coronary artery disease to 3,500 patients.

There were seven patients who had definite myocardial infarction and two others who had questionable infarction. Of these seven patients, two died suddenly while under observation in the hospital and another died five weeks after returning home. The remaining twenty patients had coronary sclerosis with angina pectoris. Two of these had a history which suggested previous myocardial infarctions, but the diagnosis could not be proved.

Of the twenty-seven patients, only one was under the age of 35 years. Thirteen of the twenty-seven patients had varying degrees of obesity. Seventeen of the patients (63 per cent) had varying degrees of hypertension. In this series there was only one patient who had diabetes. Of the five patients who were of normal weight and had infarction, four had hypertension, and the fifth had neither obesity, hypertension, nor hyperlipemia. Of fourteen patients who had blood fat determinations, eight showed elevation and six had normal values.

The results of this study confirm previous impressions that coronary disease is very rare in women under the age of 40 years.

BELLET.

Geiger, A. J., and Durlacher, S. H.: The Fate of Endocardial Vegetations Following Penicillin Treatment of Bacterial Endocarditis. Am. J. Path. 23:1023 (Nov.), 1947.

The authors concur in what is now the generally accepted fact of the curability of acute and subacute bacterial endocarditis, but they point out that the ultimate proof lies in the demonstration of complete sterility of the damaged heart valves in patients who have been successfully treated and who have died of other causes.

They give the clinicopathologic findings in four patients with endocarditis, all of whom were treated for bacteremia with large doses of penicillin. In three patients, the blood was cleared of

a *Staphylococcus aureus* infection, but death resulted in one from acute left ventricular failure in association with aortic valvulitis; in the second, from acute rheumatic myocarditis and rheumatic pneumonia; in the third, from renal failure associated with cerebral and renal abscesses. The damaged heart valves were negative for the presence of bacteria by both culture and direct stain of the vegetations. A fourth case was likewise successfully treated for *Streptococcus viridans* bacteremia, but died of an overwhelming mycotic infection due to *Monilia albicans*. The mitral stenotic lesion was studied bacteriologically (at autopsy) with negative results for streptococci.

The authors had the opportunity of observing various stages of healing in the damaged valves. The completely healed lesion is characterized by a pale, hard, smoothly endothelialized mass of dense connective tissue with areas of calcification. Thrombotic accretions have disappeared and bacteria cannot be recovered from the surface or depth of these repaired valves.

GOULEY.

Sussman, M. L.: The Differentiation of Mediastinal Tumor and Aneurysm by Angio-Cardiography. Am. J. Roentgenol. **58**:584 (Nov.), 1947.

The differentiation of aneurysms from tumors which are close to the heart and/or great blood vessels is not always possible by conventional roentgen methods. This can now be done in the usual case by angiocardiography. An aneurysm ordinarily becomes opaque along with its vessel of origin, whereas a tumor does not. In a tumor the vessels may be compressed or displaced. Otherwise, it maintains its integrity, except in those cases where it may be infiltrated with a neoplasm. In rare cases a fibrosing tumor may produce a traction aneurysm.

The angiocardiographic technique follows that described by Robb and Steinberg with the addition of multiple exposures which are made at set intervals following the injection. The rapid injection of 40 to 50 c.c. of 70 per cent Diodrast into the antecubital vein through a 12 or 13 gauge needle is made in one to one and one-half seconds. Five exposures are made at two, four, five, six, and seven seconds after the injection. Reactions to the procedure are usually transient. Severe reactions are rare and no fatality has occurred in over 1,000 cases studied by the author.

In those patients where the aneurysm has clotted, or in the case an aneurysm with a small neck the usual visualization of an aneurysm does not occur. In this event, the aorta and/or pulmonary artery may show dilatation or abnormalities in outline which may suggest the nature of the mass.

The author presents six cases in which angiocardiographic studies were of importance in the elucidation as to the nature of the mediastinal mass. This procedure is no longer of academic interest only, since many mediastinal tumors can be successfully removed by competent thoracic surgery. In a limited number of cases the differential diagnosis can be definitely made by this method.

ZION.

Fowler, N. O., Jr.: Splenomegaly in Congestive Heart Failure. Ann. Int. Med. **27**:733 (Nov.), 1947.

In uncomplicated heart failure, the spleen usually is increased above the normal size. This enlargement is proportionately greater than that of the liver in cardiac decompensation. The splenomegaly of cardiac decompensation is apparently not greatly influenced either by the duration of the congestive heart failure or by the presence of infarctions in the spleen, or by the etiological type of heart disease primarily responsible for the heart failure. In 13.4 per cent of ninety-seven cases of uncomplicated congestive failure, the spleen was found to be large enough to be theoretically palpable (weight over 300 grams). The enlargement of the spleen is thought to be the result of congestion of that organ in combination with portal hypertension resulting from some degree of cardiac cirrhosis.

WENDKOS.

Proceedings of the American Society for the Study of Arteriosclerosis

Chicago, Ill., Nov. 2 and 3, 1947

FIRST SCIENTIFIC SESSION

ANATOMIC CONSIDERATIONS IN THE STUDY OF ARTERIOSCLEROSIS

W. C. Hueper, New York, N. Y., Presiding

Round Table:

L. N. Katz, Chicago, Ill., (Moderator)
N. S. Davis, Chicago, Ill.
R. W. Kissane, Columbus, Ohio
J. C. Paterson, London, Ont.
C. Woerner, Louisville, Ky.

General Discussion:

F. W. Dunihue, Burlington, Vt. (Leader)
Margaret Bevans, New York, N. Y.
A. C. Corcoran, Cleveland, Ohio
L. Horlick, Chicago, Ill.
I. H. Page, Cleveland, Ohio
H. S. Simms, New York, N. Y.

CELLULAR PATHOLOGY OF ENDOTHELIUM*

RUDOLF ALTSCHUL, M.D., SASKATOON, CANADA

From the University of Saskatchewan

In 1944, I described the "dedifferentiation" of endothelium in human arteriosclerosis. Since then, many more observations have confirmed the view that endothelial cells may leave the vessel lining and assume features of mesenchymal cells. It also was noted that scattered among the star-shaped cells are some elements which do not branch extensively, and which have an elongated cell body, a clear cytoplasm, but have dense cell boundaries and a long oval nucleus. These cells can be distinguished in iron-hematoxylin preparations only. They may be developing fibroblasts, or may be smooth muscle cells or angioblastic cells.

In 1929, Ssolowjew described the migration of smooth muscle cells through the elastica interna into the intima of injured arteries. This phenomenon is also seen when arteries are ligated experimentally. The cells of the media, found in the intima, may retain their characteristics for an undetermined period of time, although some of them become less differentiated and then resemble cells stemming from the endothelium. It seems that such a cell migration also occurs in human and experimental arteriosclerosis, but owing to the slower development, this process is more difficult to follow.

Transformation of endothelium to foam cells in human and in experimental arteriosclerosis has not yet been well defined. Anitschkow and Klotz categorically denied such a transformation; others denied it indirectly by stating that all foam cells originate from macrophages. Wacker and Hueck, Hueper, and

*Paper not to be published in full at present.

Altschul described the foamy transformation of endothelial cells, maintaining at the same time that cells other than endothelial cells may, likewise, become foamy. The view that the endothelium takes up lipoids as a phagocytic function is difficult to correlate with our present knowledge of phagocytosis. Another possible explanation considers the foamy transformation of endothelium to be a degenerative process.

Discussion.—Woerner expressed the view, with which the members of the round table agreed, that endothelial cells may migrate and that histiocytes are probably of endothelial origin. He further suggested that new vasa vasorum may arise from the endothelium. *Paterson* stressed the importance of the ingrowth of capillaries into the arterial intima. It was suggested that tissue cultures might elucidate the problem but *Paterson*, supported by *Simms*, pointed out that, to date, endothelium has not been grown in tissue culture. *Altschul* again emphasized the "dedifferentiation" of epithelium which occurs in vitro, and mentioned the amitotic division of endothelial cells under unfavorable conditions, and the tendency of endothelial cells to contribute to the formation of vascular channels in thrombi. *Hueper* stated that histologically one can see the "birth of an atheroma"; the young proliferative endothelial cells are phagocytic but mature ones are not.

Conclusion.—The question of the origin and nature of the histiocytes in the subintima was raised but not answered. The fundamental problem is the appearance of cholesterol in the subintima.

THE PATHOGENIC PATTERNS OF ARTERIAL HYPERTENSION*

W. RAAB, M.D., BURLINGTON, VT.

From the Division of Experimental Medicine, The University of Vermont, College of Medicine

Hormonal, neurohormonal and renal-humoral pathogenic factors are involved primarily or secondarily in the common forms of arterial hypertension. The influence of these factors varies from person to person and in the same person during the course of time.

The adrenal cortex, under the regulating influence of the pituitary gland, can contribute to elevations of blood pressure through production of renal vascular sclerosis (Selye) and ischemia (renin mechanism, hydroxytyramin); through cerebral vascular sclerosis (Selye) and ischemia through a central vasoconstrictor mechanism (Nowak and Walker, Fishback and associates, and Raab); and through sensitization of the vascular system to epinephrine-sympathin (Sanders, Raab). Furthermore, cerebral ischemia is capable of mobilizing epinephrine.

Increased secretory activity of the adrenal medulla (as in pheochromocytoma which imitates all vascular, cardiac, renal, ocular, and metabolic features of essential hypertension) is capable of producing direct vasoconstriction, as well as of eliciting central and renal hypertensive mechanisms. This probably involves metabolic anoxia in the brain and the kidneys due to the action of epinephrine (Blix, Ahlgren, Roest). In the absence of a medullary tumor, analogous effects can be produced by exaggerated sympathin discharge from postganglionic fibers into the contractile effector cells of the cardiovascular system (Raab and Humphreys). The brain produces and discharges into the cerebrospinal fluid a vasopressor sympathomimetic amine, encephalin (Raab), which may also contribute to hypertension.

Examples of types of hypertension, originating primarily in the organs enumerated, are: (a) pituitary; (Cushing's disease), (b) adrenal (cortical and

*Paper not to be published in full at present.

medullary tumors), (c) brain (concussion, trauma, encephalitis), and (d) kidney (polycystic kidney, pyelonephritis, obstruction of renal artery).

In "essential" hypertension the hormonal and neurohormonal factors usually prevail in the earlier stages; the secondary sclerotic, ischemia-inducing factors, including those eliciting renal humoral mechanisms, follow later.

Discussion.—Not less than twelve factors were enumerated in the development of hypertension. The roles of sympathin and of a cerebral hormone in the intricate mechanism of the genesis of hypertension were stressed. Dietary restrictions of salt and of animal fats were advocated. The opinion of the members of the round table and discussion was divided on all matters. *Woerner* and *Kissane* thought the idea of a cerebral hormone too hypothetical and the role of sympathin overstressed, while *Dunihue* mentioned the possibility that secretory cells might be present in the hypothalamus. *L. Katz* held sympathin to be a nonspecific substance. *Page* recalled that many compounds can be extracted from the brain, some of which are depressors while others are not. Several years ago he extracted a strong pressor substance from cerebral ventricular fluid. *Kissane* was inclined to see a moderate degree of cerebral arteriosclerosis as cause of hypertension, but *Paterson* pointed out that there is no parallelism between cerebral findings and hypertension. *L. Katz* then directed attention to the fact that renal hypertension still dominates the picture. *Dunihue* thought that renal ischemia in combination with systemic anoxemia might be the causative mechanism of hypertension. *Page* and *Hueper* stated that renal ischemia appears late, and not early, in the course of the disease. Therefore, it is improbable that it is a pathogenetic factor. *Page* stressed that the humoral hemodynamic equilibrium is disturbed in essential hypertension. There is arteriolar constriction (not caused by pitressin) and increased cardiac effort without increased output (not caused by epinephrine). *Corcoran* mentioned that desoxycorticosterone is not normally present in adrenals. *Davis* thought that endocrine glands are involved in the causation of hypertension and pointed out the frequency of cortical adrenal metaplasia and adrenal dysfunction, primary or secondary to pituitary disorder. He further thought that cortical steroids may interfere with the renal metabolism but finally conceded that endocrine change may be due to nutritional failure. In the matter of therapy, *Kissane* opposed any dietary restriction.

Raab defended sympathin as specific for hypertension and a substance he calls encephalin, which is closely related to sympathin and to epinephrine, as shown by biologic and colorimetric tests. He conceded that encephalin might be identical with the vasopressor-central nervous system exciting substance of *Page*.

Conclusion.—The question of hypertension requires much further penetrating investigation before speculation should be indulged in too much. The problem is many-sided and therefore susceptible to a wide variety of attacks. Most important is that suggested mechanisms be adequately supported before they be offered as common coinage.

VASCULARIZATION OF THE AORTA IN DIFFERENT SPECIES IN HEALTH AND DISEASE

J. G. SCHLICHTER, M.D., CHICAGO, ILL.

From the Cardiovasular Department, Research Institute, Michael Reese Hospital, Chicago

The vascularity of the aorta in dogs, chickens, rabbits, and men was studied by an injection technique with a radiopaque mixture. This disclosed the presence of vasa 10 μ or more in diameter. The aortas were x-rayed and sections were prepared.

The most marked vascularity of the aorta is found in dogs. The next most conspicuous vascularity is in man and vascularity in chickens is less pronounced. Rabbits have the poorest vascularity.

In dogs, an extensive adventitial and less extensive medial plexus are joined by vasa which arise from the lumen of the aorta. The plexi are supplied by vessels arising from branches of the aorta. The first vasa arise from the coronary arteries. The adventitial plexus becomes less extensive as one progresses from the ascending to the descending aorta. The reverse is true of the number of vasa arising from the lumen of the aorta. No intimal plexus could be visualized. In the other species studied, the adventitial plexus alone was found.

The aortas of infants showed the most marked vascularity. This decreases relatively with the increased size of the growing aorta.

Experimental interference with the vascularization of the ascending aorta in dogs through coagulation of the adventitia led to cystic necrosis of the media, spontaneous rupture and dissecting aneurysm, proliferation of the intima, and fibrotic changes. In a hypertensive dog a true, small aneurysm was produced. These changes were observed after periods of from six hours to six weeks.

Coagulation of the adventitia with addition of cholesterol feeding (5.0 Gm. of cholesterol in cottonseed oil daily), intraperitoneal injection of a cholesterol emulsion (1.0 Gm. of cholesterol as a 2 per cent emulsion), and thiouracil feeding (0.5 Gm. daily) produced atheromatous lesions in the ascending aorta.

Below atheromatous plaques, the human aorta is less vascular. In fibrotic areas, secondary vasa 10 to 30 μ wide are seen in man and dog. Newly formed vasa of intimal origin are present in atheromatous lesions in man as well as in experimental cholesterol-induced atheromatosis of chickens.

The differences in the vascularity of the aorta in these species may explain the difficulty of inducing medial necrosis or arteriosclerosis in dogs and the ease with which these changes are produced in rabbits. Men and chickens occupy a position between the two extremes. Variation in vascularity in different sectors may be related to the marked preponderance of lesions in the descending aorta.

Cholesterol plays an important role in producing atheromatosis.

Discussion.—No controversy was aroused by this presentation. *Paterson* inquired why a finer suspension of dye was not used to visualize the smallest vessels. *Schlichter* replied that in his study interest centered on the larger vasa vasorum. A gelatin-lead carbonate-mercuric sulfide mixture, described by Dock, was used for injection. He added the information that necrosis of the media and intimal lesions were seen above areas of normal adventitia if these areas belonged to the supply of coagulated vessels and had insufficient collaterals.

Hueper pointed out that the vascular problem of various species had been studied by Fox: species with low vascularization tend to atheromatosis; the other species, to damage of the media. He thought that atheromata of the veins were rare because of their better developed vasa vasorum.

Conclusion.—Vascularization of the aorta, which varies widely in different species, is a decisive factor in localization of atheromatous lesions and may play a role in their development.

MEDIAL DEGENERATION AS THE PRIMARY LESION IN CORONARY SCLEROSIS IN CHICKENS*

J. C. PATERSON, M.D., S. J. SLINGER, M.S.A., AND K. G. GARTLEY, B.S.A., ONTARIO, CANADA

From the Department of Pathology, University of Western Ontario, and the Department of Poultry, Ontario Agricultural College

The observations reported were made in the course of a series of long-term studies on cholesterol arteriosclerosis of the coronary arteries of chickens. Routine examination of the coronary arteries of cholesterol-fed and control birds in the earlier stages of the experiments, has revealed: (1) a medial lesion which appears to be of prime importance in the genesis of coronary sclerosis in chickens; (2) that the incidence of coronary sclerosis of the intimal variety is almost as great in the control birds (75 per cent) as in the cholesterol-fed birds (82 per cent); and (3) that cholesterol feeding markedly accelerates the coronary sclerosis in our experimental birds.

These observations were made on the hearts of thirty-three White Leghorn cockerels, sacrificed from three and one-half to twelve months after the start of feeding with 2 per cent dry cholesterol, and on the hearts of thirty-three control birds of the same strain and age fed only the basal diet. The upper two-thirds of each heart was subjected to serial section at intervals of 400 microns. This provided approximately twenty-five equidistant sections, each containing three major coronary branches, from every specimen. The primary nature of the medial lesion was demonstrated by complete serial section of an early lesion in a coronary artery of a control bird. The observations in White Leghorn cockerels have been confirmed in Barred Rock cock birds in a second experiment.

It is concluded that, under the conditions of the experiments, (1) cholesterol feeding accelerated but did not cause the coronary arteriosclerosis in our two strains of chickens; and (2) a medial degenerative focus was responsible for the initial proliferation of the intima of the coronary arteries in these birds.

Experiments designed to elucidate the cause of the primary medial lesion in chickens are in progress.

Discussion.—A very unexpected feature of arteriosclerosis in cockerels was brought out by this paper: the primary medial change. This had not been observed by *L. Katz* and *Horlick*, who also used chickens as experimental objects. However, their birds were sacrificed when three to four weeks old, whereas *Paterson's* birds were three and one-half months old at the time of his observations. *Katz* and *Horlick* commonly observed intimal changes within one and one-half weeks. Since it is true that dry cholesterol must be fed for a much longer period of time than if cholesterol in cottonseed oil is administered, the vehicle might modify the results of experiments. The latter method elevated blood cholesterol of chickens from 1,000 to 1,500 as against 400 to 500 mg. per 100 ml. after dry cholesterol feeding. In this connection, the importance of the additional diet, especially of butter fat, was pointed out by *Davis*. *L. Katz* brought out the fact that commercial cholesterol, at present, is of inferior quality, containing in some cases only 10 per cent of cholesterol. *Paterson* replied that he used Armour's product which appears to be satisfactory.

Conclusion.—There are obvious difficulties in comparing the results of seemingly analogous experiments. It appears doubtful that the chicken is a better experimental subject for the study of atheromatosis than the rabbit.

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*Paper in print, Arch. Path.

A STUDY OF THE BLOOD LIPIDS IN OMNIVOROUS ANIMALS

J. B. STUBBS, M.D., E. LEE SHRADER, M.D., AND
G. O. BROUN, M.D., ST. LOUIS, MO.

From the St. Louis University Hospital

Male albino rats, 3 weeks of age, were fed a diet of Purina laboratory chow. To the diet of one series of twenty rats was added 10 per cent, by weight, of cholesterol. To the diet of another group of ten rats 1 per cent thiouracil was added. A control series of ten animals was maintained on laboratory chow alone. The experimental and control diets were continued for eighteen weeks. At the end of this period the animals were sacrificed.

Gross inspection of the aortas of the experimental animals did not reveal lesions of sufficient size to allow detection. Microscopic study of the sections stained with Sudan IV showed small lesions, which were interpreted as being early atheromas in four of ten animals receiving thiouracil and in seven of twenty animals receiving cholesterol. None were found in the control animals receiving basic diet alone. These lesions consisted of palisading of intimal cells which contained pink-staining particles of various sizes, and in a number of instances an accumulation of large clear cells with pink-staining particles interpreted as being the foam cells described by Leary and Hueper.

The average free blood cholesterol of the three groups were: control series, 30 mg. per cent; thiouracil series, 28 mg. per cent; and cholesterol series, 58 mg. per cent. The cholesterol esters of the control group average 74 mg. per cent; those of the thiouracil-fed animals, 79 mg. per cent; and of the cholesterol-fed animals, 83 mg. per cent.

Selecting only those animals in which atheromatous lesions were found, in the thiouracil-fed animals free cholesterol was 16 mg. per cent, and cholesterol esters were 83 mg. per cent. In the cholesterol-fed animals showing aortic lesions, free cholesterol was 58 mg. per cent, and cholesterol esters, 83 mg. per cent.

We therefore found a moderate increase over the normal controls in cholesterolesters in the entire group of cholesterol-fed animals and in those fed thiouracil which showed atheromatous lesions.

Discussion.—This presentation proved highly controversial, perhaps because no slides of atheromatous lesions in rats were shown. *L. Katz* and *Horlick* pointed out their failure to demonstrate such lesions although cholesterolemia up to 250 mg. per 100 ml. was produced by feeding rats cholesterol alone and up to 500 mg. per 100 ml. when thiouracil was administered in addition to cholesterol. *Paterson* inquired about the technique by which the heart of a rat can be weighed accurately. *Stubbs* emphasized that the aorta was cut off rather close to the heart. He stated that aortic lesions which gave a positive staining reaction with Sudan IV were considered positive evidence of atheromatosis.

Conclusions.—The fact that the rat cannot be recommended as an animal for the study of experimental atheromatosis obviously was known to the discussors and others in the audience. It was agreed that much effort would be conserved if negative results of experimental and clinical observations were reported (in a "Journal of Negative Information" as suggested by *L. Katz*).

SECOND SCIENTIFIC SESSION

PHYSIOLOGIC CONSIDERATIONS IN THE STUDY OF ARTERIOSCLEROSIS

Irvine H. Page, Cleveland, Ohio, Presiding

Round Table:

A. C. Corcoran, Cleveland, Ohio (Moderator)
E. C. Andrus, Baltimore, Md.
M. Bruger, New York, N. Y.
R. A. Katz, New Orleans, La.
M. F. Root, Boston, Mass.
A. G. Saidman, Washington, D. C.
H. Selye, Montreal, Canada

General Discussion:

L. N. Katz, Chicago, Ill. (Leader)
W. C. Hueper, New York, N. Y.
R. W. Kissane, Columbus, Ohio
M. H. Knisely, Chicago, Ill.
J. C. Paterson, London, Ont.
L. L. Waters, New Haven, Conn.
J. B. Wolffe, Philadelphia, Pa.

RENAL VASCULAR AND DIODRAST Tm CHANGES WITH AGE*

DEAN F. DAVIES, M.D., BALTIMORE, MD.

From the Section of Gerontology, U. S. Public Health Service

Evidence has accumulated from several sources that the kidney undergoes both an absolute and a relative atrophy during the aging process. Studies of kidney function in eighty-five men between the ages of 20 and 90 years, without clinical history, signs, or symptoms of renal or cardiac disease, show a marked decrease of diodrast clearance, inulin clearance, and diodrast Tm with age. This indicates a decreased effective renal blood flow, glomerular filtration rate, and tubular excretory capacity with age.

Whether (1) the decreased effective renal blood flow is secondary to a vascular defect such as arteriosclerosis from which atrophy of parenchymal tissue results, (2) "senile atrophy" of parenchyma is followed by secondary sclerosis or decrease of vascular supply, or (3) both the vascular supply and the parenchymal function decrease together can be judged by the degree of change occurring in each function.

The fact that the effective renal blood flow per unit of tubular capacity decreases with age strongly suggests that there is a primary vascular defect accompanied by a dependent atrophy of parenchymal tissue. That this change is statistically significant is shown by a critical ratio for the difference of means between the 20 to 50 year and 60 to 90 year age groups of 5.44. Whether this decrease of effective blood flow is a result of decreased cardiac output, arteriosclerosis, or some other vascular defect is not known, but a rise in filtration function with age indicates an alteration in intrarenal hemodynamics.

Discussion.—This paper provoked a shower of questions. *Bruger* and *Corcoran* wanted to know the blood pressure levels, and the balance of the hydrostatic and osmotic pressure in the kidney. *Corcoran* and *Selye* asked about the relation to anatomic alterations. *R. Katz* stressed the desirability of the histochemical approach in gerontologic studies. *Root* asked for information about the weight loss of the patients, their previous condition, their total blood volume. *Saidman* thought that estimation of the maximum specific gravity of the urine and also of the urea clearance may give almost the same information

*Paper not to be published in full at present.

for clinical purposes as the diodrast clearance test. He was seconded by *Corcoran*. *Andrus* brought up the problem of "normals," stressing that frequently "normal values" are compiled from information gathered from institutionalized persons. *Davies* replied that normal values were obtained by the study of persons who were subjectively and objectively without signs and symptoms of disease, and whose blood pressure, electrocardiogram, and urine were normal. Only two or three out of every one hundred persons were suitable to be used as controls. There is wide variation in blood pressure of older people, but the findings reported pertain to a selected group. The number of functioning glomeruli decreases with age in different species and with this, the rate of blood flow and the glomerular filtration.

Conclusion.—The obvious question must be asked: What diagnostic criteria should be used in nephropathies in the aged if there is a physiologic functional renal deficiency with advancing age? This query opens an important field for investigation.

REDUCED NUTRITION OF THE VESSEL WALLS AS RESULT OF INTRAVASCULAR AGGLUTINATION*

MELVIN H. KNISELY, PH.D., CHICAGO, ILL.

From the Hull Laboratory of Anatomy, University of Chicago

The purpose of this presentation is to call to the attention of this association certain combinations of pathologic physiology which may very well be initiating, contributing, or maintaining factors in at least some cases of human arteriosclerosis.

O'Neill (Ann. Surg. **126**:270, 1947) working in Drinker's laboratory has recently found and clearly demonstrated that shutting off the flow of blood through the vasa vasorum which nourish the walls of large vessels of dogs initiates the disintegration of the lining of the lumen of the large vessel. Stated as a generalization, he has found that adequate flow of blood through the vasa vasorum is necessary for the maintenence of intact, healthy, normally functioning linings of the large vessels.

By microscopic observations of a statistically valid sample of the circulating blood of human beings, members of our laboratory (Science **106**:431, 1947) have found that the circulating blood of about 600 human hospital patients having about fifty different diagnoses was agglutinated into masses large enough and rigid enough so that they forcibly resisted passage through all visible terminal arterioles.

If the dimensions of living human vasa vasorum are of the same order of magnitude as those of all previously studied smallest living vessels of animals and men, the changing of the blood to a sludge must forcibly reduce the rates of flow of blood through all the open vasa vasorum of the human body.

In some sludges, consisting of masses of mixed sizes, masses large enough to embolize small vessels are slowly showered into the arterial system. (A motion picture showing normal unagglutinated blood and several types of sludged blood was projected.)

It seems quite probable that various degrees of forcible reduction in nutrition of vessel walls, including embolization of vasa vasorum, should now be studied to determine the frequency and degree to which these factors contribute to vessel wall pathology. Technical methods adequate to begin such studies are now available.

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*Paper has been published in full length in Science.

Discussion.—The observation reported illustrated to *Corcoran* how the same picture is viewed differently by different people. In addition to post-traumatic conditions, the study should be extended to normal people who fall ill. *Root* found a similarity to the hemoglobin precipitation in renal tubules (lower nephron nephrosis), in burns, and in the crush syndrome. *Corcoran* raised the question whether agglutination is not due to plasma protein changes and asked whether intravascular agglutination of erythrocytes is due to slowing of the blood flow or whether the blood flow slows down because of agglutination. *Wolffe* recalled that there are many reasons for intravascular clotting. *L. Katz* inquired about the collaterals in occlusions, about the rate of agglutination, and, especially, about the elasticity of vessels. He wanted to know which part of the clotting mechanism is altered in these patients.

This and many other questions cannot be answered at the present time. What is the mechanism of pain in vascular occlusions? How do arteriosclerotic changes affect the nutrition of tissues, how do they affect enzymes and hormones? *Waters* thought that while one might refuse to accept the theory of development of arteriosclerosis due to intramural hemorrhages, one cannot deny the importance of vasa vasorum circulation in this connection. *Hueper* mentioned his work with polysaccharides which, if agglutinated due to viscosity changes, produce arterial lesions similar to cholesterol atheromatosis.

According to *Knisely*, there are various types of agglutination: homogeneous, with even-sized particles; and nonhomogeneous, with unevenly sized constituents. The flow slows first, the agglutination is secondary. The coagulability of the blood is not always the same, at least not in monkeys. However, the methods available to study coagulation are not reliable. Microscopic observation renders the best results.

CHANGES IN THE COAGULABILITY OF THE BLOOD IN ARTERIOSCLEROSIS OBLITERANS OF THE EXTREMITIES*

NELSON W. BARKER, M.D., ROCHESTER, MINN.

From the Department of Medicine, Mayo Clinic

Pathologic examination of arteries in legs amputated because of advanced arteriosclerosis obliterans shows that thrombosis is responsible for at least part of the occluding process in the arteries in all these patients. There is considerable variation in the relative extent of atheroma and thrombosis in different cases. It is logical to assume, therefore, that thrombosis may occur only where there is extensive atheroma with degeneration of the overlying endothelium in some individuals, whereas thrombosis may occur with a minimal amount of atheroma and a minimal amount of degeneration in other individuals. This has raised the question as to whether or not there may be measurable changes, in the direction of increased coagulability, in the blood of some patients with arteriosclerosis obliterans.

Studies have been made of the blood of patients with arteriosclerosis obliterans with the use of the following tests: Hagedorn modification of de Takats' heparin tolerance test; coagulation time of heparinized blood in vitro (Rosenbaum technique); coagulation time of whole blood in silicone-coated tubes; measurement of antithrombin activity of the serum (Astrup and Darling technique); and the Quick prothrombin time determined with the use of both undiluted and diluted plasma. The results of these tests have indicated that an appreciable number of patients with arteriosclerosis obiliterans have low heparin tolerance, and that an abnormally rapid congulation time of their blood occurs

*Paper not to be published in full at present.

when it is heparinized in vitro. Determinations of antithrombin have been variable, the average determination being the same as it is among normal persons, but the extremes being both greater and less than normal. The tests of prothrombin time of both diluted and undiluted plasma have not revealed appreciable differences from normal figures. Coagulation times determined from blood in silicone tubes have been shorter than normal to some cases.

Discussion.—This presentation stimulated *Corcoran's* question as to whether hypoheparinemia might explain some thrombotic states. Nobody knew the answer. *Bruger* stated that the blood fibrinogen increases up to 0.8 per cent in every instance of coronary thrombosis and *Saidman* pointed out that the blood coagulation time is shortened in arteriosclerosis with thrombosis in nondiabetics and in diabetics as well. He recommended a six weeks' treatment with Dicumarol to maintain a coagulation time of about 25 seconds. *Root* warned of reactions to Dicumarol in diabetic patients; these should be given only one-half to one-third the usual dose. *Corcoran* refused rutin as treatment of thrombosis. His statement was applauded by the audience. *Andrus* inquired as to whether laboratory tests were performed before or after thrombosis. In answer, *Barker* said that tests were done after the vascular occlusion. It is hardly possible to test large groups and then wait for thrombosis to occur. It seems questionable whether or not there is a heparin deficiency in patients with thrombosis. Some unknown substance may neutralize heparin, or there might be too little of it produced. Fibrinogen assays are difficult and also its amount oscillates considerably from day to day. Silicone apparatus for estimation of the coagulation time is superior to glass apparatus. Repeated tests should be done on large series of people.

Conclusions.—The search for a laboratory method to determine threatened thrombosis in patients with arteriosclerosis must continue, as none of the many methods available at present is reliable.

THE EFFECT OF ARTERIOSCLEROSIS ON THE DYNAMICS OF HYPERTENSION IN THE AGED

FREDERIC D. ZEMAN, M.D., AND B. M. SCHWARTZ, M.D., NEW YORK, N. Y.

From the Medical Service in the Home for Aged and Infirm Hebrews, New York

In an effort to clarify some of the problems associated with hypertension and arteriosclerosis in older persons, the clinical and post-mortem findings in 150 men and women from 58 to 92 years of age were studied. While the number of cases in the series is small, we believe that the application of this classical method will ultimately lead to increased understanding.

As age advances, there is a tendency for peripheral resistance to increase, for aortic elasticity to decrease, for aortic volume to increase, and for cardiac output to decrease. The blood pressure will reflect which of these factors predominate. Most often a "normal" blood pressure in old age is not evidence of a normal cardiovascular system, but is the resultant of several of these factors acting in opposite directions.

"Systolic hypertension" is not to be sharply distinguished as a special form of elevated blood pressure, entirely normal for old age, and benign. Its presence, for example, is associated often enough with coronary artery disease that coronary occlusion in women is as frequent in this group as in the systolic and diastolic hypertensive groups.

Systolic and diastolic hypertension in old age appears to make the persons who manifest it more liable to cerebral accidents and adds a burden to the heart, but the almost universally concomitant changes in the aorta make this type of hypertension less severe than in early life.

Malignant hypertension is absent in the aged. The level of blood pressure in old age should not be taken as an index of pathologic involvement of the vascular system but should be supplemented by studies to determine cardiac, cerebral, and renal function, and the degree of elasticity and dilatation of the aorta. Exact physiologic measurements of the cardiac output and peripheral resistance would be particularly desirable.

Discussion.—Hypertensive patients were classified into four groups: normotensive; systolic; systolic-diastolic; and undetermined types. *Corcoran* approved this grouping. He pointed out the wide variability of the blood pressure in the old and the young as well; arteriosclerotic hypertension, paradoxically, shows the maximum variation. *L. Katz* underlined that the various types of hypertension must not be confused. The important question, how to distinguish between cardiac output and flow, has not yet been answered. *R. Katz* added that in the treatment of vascular disorders with vasodilatation, attention need not be paid to the blood pressure.

Conclusions.—Variability of the blood pressure in normal and diseased old people and in arteriosclerotic young persons was emphasized. Classification of hypertensive patients for practical purposes is desirable; even so, such grouping may not always conform to theoretical considerations.

IS ATHEROSCLEROSIS WITH THROMBOTIC ARTERIAL OCCLUSION AN INDUSTRIAL DISEASE?*

NATHAN SMITH DAVIS, III, M.D., CHICAGO, ILL.

From Northwestern University Medical School

Under the occupational disease acts of the several states, many awards are being made to those claiming that unusual exertion, the more arduous aspects of their regular work, or exposure to extreme heat, cold, or to other industrial hazards caused the coronary or cerebral thrombosis, symptoms of which first appeared while the patient was at work.

Unusually prolonged and hard physical work, especially when performed at extremely low temperatures, may cause acute coronary insufficiency without thrombotic occlusion. There is, however, no evidence that hard labor has any connection with the development of atherosclerotic lesions, the rate at which they become the cause of thrombus formation, or with the initiation of thrombus formation in the cerebral, coronary, or other arteries.

The incidence of atherosclerosis is not affected by occupation. Coronary and cerebral thromboses generally occur during rest, sleep, or when those affected are doing light work; rarely when they are engaged in any task requiring unusual exertion. It appears, therefore, that atherosclerosis with thrombotic occlusion of an artery is not an industrial disease. Coronary heart disease and coronary thrombosis with cardiac infarction are seen at least as frequently in executives, professional men, and white collar workers as in laborers.

If people who are completely disabled because of diseases due to natural causes were entitled to such benefits as they would attain when eligible for old age insurance benefits, claims that atherosclerosis was an occupational disease or that thrombotic arterial occlusion was initiated by unusual physical exertion would become less and less frequent and these conditions would no longer be considered as being connected with occupation. This would make it much easier for the older age group to retain and obtain employment and would lessen the social and economic problems of the ever increasing numbers of unemployed older men and women.

*Paper to be published in full length in Indust. Med.

Discussion.—In disagreement with the speaker, *Selye* and *Andrus* agreed that stress is important. *Selye* cited the example of nightwatchmen who have a peaceful occupation for their old age. He pointed out the difficulties of statistical studies and their interpretation and accentuated that patients with cardiovascular disorders should not be handled as a single group. *Corcoran*, on the other hand, did not see any relation between exercise and thrombosis. *Selye* then wanted to hear *Knisely's* opinion in this matter. The latter supported *Davis'* views because 75 per cent of the monkeys used in his studies developed thrombosis while inactive. *Saidman* and *L. Katz* refused to accept classification of physicians as an "easy" working group. *L. Katz* remarked that emotional stresses are at least as important as physical exertion. *Paterson* considered emotion a factor in the development of coronary thrombosis, but pointed out the difference in individual reactions. *Wolffe* spoke of "effort angina" which might lead to frank coronary thrombosis up to six months after an attack. In a snow storm three times as many coronary accidents occur in man than under other circumstances. *Kissane* agreed that a releasing trauma might confuse the issue. He stressed with *Corcoran* the importance of this question in medicolegal and insurance matters. *Waters* inquired about the frequency of vascular accidents during sleep when the coronary blood flow is slower, the blood pressure is lower, and the heart work greater. *Root* spoke about geographic and climatic differences in the incidence of cardiovascular disease. He held blood cholesterol and calcium estimations diagnostically essential. *Corcoran* reminded that in former years plumbism and arterial disease were thought to be related. *Davis* maintained that control of carbon tetrachloride and other industrial poisons might prove an effective prevention of vascular disorders.

Conclusions.—The perennial controversy as to whether stress has to do with cardiovascular disease has been revived. Opinion was divided on the issue of causation of disease as well as of provocation of complications, expecially of thrombosis, in existing disease by undue stress.

THIRD SCIENTIFIC SESSION

METABOLIC CONSIDERATIONS IN THE STUDY OF ARTERIOSCLEROSIS

O. J. Pollak, Wilmington, Del., Presiding

Round Table:

H. S. Simms, New York, N. Y. (Moderator)

N. Barker, Rochester, Minn.
L. Morrison, Los Angeles, Calif.
J. B. Stubbs, St. Louis, Mo.
J. B. Wolffe, Philadelphia, Pa.

General Discussion:

I. H. Page, Cleveland, Ohio (Leader)

W. B. Kountz, St. Louis, Mo.
W. Rabb, Burlington, Vt.
M. M. Zuzman, Johannesburg, S. A.

STUDIES ON THE FAT DEPOSITING MECHANISM*

HENRY S. SIMMS, PH. D., AND MARY S. PARSHLEY, PH.D., NEW YORK, N. Y.

From the Department of Pathology, College of Physicians and Surgeons, Columbia University

By using tissue culture methods to observe the formation of fat granules in adult chicken aorta fibroblasts, it has been found that adult plasma contains

*Paper has been published in full length in J. Gerontol.

some lipid substances which we call "lipfanogens." These substances are taken up by living cells and are converted into visible fat granules. Segments of adult arteries, when treated in vitro with these lipfanogens, have been found to develop fat deposits similar to those which occur spontaneously in atherosclerosis. Therefore, the lipfanogens are thought to play a role in the deposition of fat in atherosclerosis.

Blood serum also contains an agent which opposes the formation of fat granules in the presence of lipfanogens. This agent is called "antilipfanogen." It is associated with the albumin fraction of serum proteins and is inactivated by heating at 100° centigrade.

The concentrations of lipfanogens and of antilipfanogen in a sample of serum are assayed as follows: The serum is diluted with seven parts of water. One portion is heated at 100° C. while another portion remains unheated. Concentrated physiologic solutions are added to both portions. Then these solutions are placed on specially prepared tissue cultures of adult chicken aorta fibroblasts free from fat granules. After two days' incubation, the extent of fat granule formation is observed. The amount of lipfanogens is measured by the fat deposited from the heated serum. The amount of antilipfanogen is computed from the difference between the two portions in their fat depositing action. Both portions contain identical concentrations of lipfanogens, but the unheated portion also contains antilipfanogen.

The action of antilipfanogen seems to result from a tendency to combine with lipfanogens in such a way as to interfere with the formation of fat granules.

Sera of all species which have been tested contain both lipfanogens and antilipfanogen. The balance between these two agents is believed to control, in part, the tendency to deposit fat in intimal sclerotic plaques.

Discussion.—This work earned particularly favorable comment from *Page*. *Morrison* asked about the relationship of neutral fat and cholesterol in cultures. *Wolffe* agreed with *Simms* that early pin-point atheromatous lesions should be studied chemically. *Simms* believed that such lesions contain collagen and diffusely spread neutral fat, while cholesterol might enter secondarily. *Barker* inquired about the technical difficulties of the assay of antilipfanogen, about studies of the effect of estrogenic and androgenic substances upon tissue cultures, and also about the content in serum of patients with early atheromatosis. *Simms* stated that the method is laborious. Insufficient work has been done as yet with material from patients. No studies of the effect of the sex hormones have been attempted. Thyroid effects a rise in antilipfanogen in tissue cultures, while lipocaic and similar agents do not.

Conclusion.—This fundamental study of the lipid metabolism in tissue cultures is opening a wide field for research, including studies of enzymatic lipid metabolism and atheromatosis.

DIABETES AND ARTERIOSCLEROSIS IN YOUTH*

HOWARD F. ROOT, M.D., BOSTON, MASS.

From the Deaconess Hospital, Boston

It is well known that the frequency of arteriosclerosis in older patients with diabetes is almost unequalled by any other disease. The incidence of such lesions in youthful diabetic patients is not yet fully appreciated. Lately, the number of young diabetic patients who develop premature arteriosclerosis during the third decade of life has been stressed. Among 110 deceased diabetic subjects (1938

*To be published in full length.

through 1946) were ten whose diabetes had begun before the age of 20 years and two with onset at 22 and 27 years, with diabetes of 0.2 to 20 years' duration. Seven who died at ages between 25 and 32 years had coronary arteriosclerosis with partial or complete occlusion, while renal arteriosclerosis was present in six of the seven, and intercapillary glomerulosclerosis in three. In youthful patients with diabetes of more than ten years' duration, all three common types were present: (1) Mönckeberg's sclerosis of the media; (2) aortal and coronary atheromatosis; and (3) arteriolar sclerosis, especially renal. There is clinical evidence of premature arteriopathy in youthful diabetics after fifteen or more years of the disease. Of 154 patients who had developed diabetes before the age of 15 years and had survived twenty years of diabetes, examined by x-ray, 106 had demonstrable vascular calcification of the legs.

A nutritional factor may contribute to the development of arteriosclerosis in youth, as lesions were found only in those uncontrolled by diet over a period of years. Lipemia and hypercholesteremia commonly occurred before the use of insulin and are not rare now in inadequately treated patients. Among diabetic patients with onset of the disease in childhood who had survived twenty years of diabetes, 50 per cent of those now incapacitated by coronary, renal, or retinal arteriosclerotic lesions had had diabetic coma repeatedly. Only 10 per cent of patients showing no arteriosclerosis had had coma.

In no case has arteriosclerosis been present at the time the child's diabetes began. If the development of arteriosclerosis were due to an inherited inferiority, one would expect that vascular alterations in some instances would occur before, or at least at the same time as the diabetes. Vascular disease develops only after diabetes of many years' duration; its severity is related to the degree of control of the diabetes. Not all diabetic patients are doomed to develop retinal hemorrhages or premature vascular disease.

Discussion.—The great tendency of diabetic patients to develop atheromatosis was demonstrated. *Barker* stated that the vascular complications of diabetic subjects are similar to lesions encountered in nondiabetic subjects. *Stubbs* thought that syphilis and myxedema have as important a relation to atheromatosis as diabetes mellitus and inquired whether any of Root's patients had hypothyroidism. He wanted to know the weight of these patients. *Root* replied that only a single individual of his series had myxedema, another developed it five or six years after onset of diabetes. He emphasized that the basal metabolic rate tends to rise in diabetic children and that hypercholesteremia occurs with acidosis. *Barker* pointed out that elevation of the blood cholesterol is not constant in diabetic subjects and *Zuzman* held hypercholesteremia rare in such patients, just as the incidence of hypertension is. These statements were made in answer to *Morrison's* question about the treatment of hypercholesteremia. *Raab* claimed that the anterior pituitary lobe is involved in diabetes and that the amount of sympathin, the oxidation catalyst, increases with age. *Wolffe* wanted to hear more about the juvenile diabetic patients who remained well for twenty to twenty-five years after onset of diabetes. *Root* could not give a reason for the well-being of twenty-two patients out of 200, all of whom were carefully studied by x-ray of the legs, pelvis, and aorta and by examination of the eye grounds. They were free of arteriosclerosis, retinal hemorrhages, albuminuria, or hypertension. A single vascular complication detected by x-ray or with the ophthalmoscope was found in twenty-eight additional patients.

Conclusion.—There is an abnormally high incidence of arteriosclerosis early in life among patients with diabetes mellitus. Further investigation of pathologic and precocious aging in diabetics is needed, as is the interrelation of insulin and lipid metabolism.

STUDIES OF THE EFFECT OF LIPOTROPIC AGENTS IN EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS IN THE RABBIT*

G. O. Broun, M.D., K. R. Andrews, M.D., and P. J. V. Corcoran, M.D.
St. Louis, Mo.

From the Department of Internal Medicine, St. Louis University School of Medicine

Various lipotropic substances such as lipocaic, choline, betaine, methionine, and inositol were administered to rabbits receiving a standard diet with the addition of 0.5 Gm. daily of cholesterol. Daily dosage of 500 mg. of choline, and even of 75 mg., offered some protection against the development of atherosclerosis. Doses of 40 to 10 mg. of choline chloride, while somewhat effective in rabbits 3 months of age, failed to protect animals 6 to 8 months of age.

Several lots of lipocaic were prepared according to the directions of Dragstedt, Van Prohaska, and Harms. Additional lots were obtained from Eli Lilly and Company. All preparations contained choline in varying amounts. Groups of animals were given pure choline chloride in amounts equal to the choline content of the lipocaic preparations tested.

Of the various lots of lipocaic some were entirely or practically ineffective. Other preparations appeared to have some protective value and prevented atherosclerosis under the conditions of the experiment. Some preparations appeared to protect the aorta in greater degree than could be accounted for on the basis of their choline content.

Betaine and methionine, in dosages four times as great, appeared roughly equivalent to choline. Inositol in the dosage employed had no demonstrable effect on either the aorta or the liver. Some lots of pancreatic extract appeared to prevent the rise of blood cholesterol after cholesterol feeding. Prevention of atherosclerosis by these extracts was not directly related to the prevention of the rise of blood cholesterol.

Discussion.—The difference in the action of various lipotropic substances has been illustrated. *Wolffe* agreed with *Barker* that the name "lipocaic" should be discarded because of the different nature of preparations. He further advocated the term "tissue extract" instead of "pancreatic extract." The effectiveness of these extracts is apparently due to variation in choline content. Thus, some extracts were ineffective and some even gave rise to hypercholesteremia. *Morrison* stressed the importance of proper dosage of choline: 1,000 mg. should be given therapeutically instead of the commonly used dose of 500 milligrams. *Stubbs* and *Wolffe* then pointed out that in human beings the blood cholesterol level decreases after lipocaic and other substances for weeks but that the effect is temporary.

Conclusions.—The administration of pancreatic extracts is useless for experimental purposes unless their choline content is known. Pure choline might well replace these preparations. Neither are curative in atheromatosis as they aid only in the removal of lipids from the liver but not from vascular depots.

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*Paper to be submitted to the J. Gerontol. for publication in full length.

THYROID AND EXPERIMENTAL ATHEROSCLEROSIS IN THE CHICKEN

L. HORLICK,* M D., D. DAUBER,† M.D., AND L. N. KATZ, M.D., CHICAGO, ILL.

From the Cardiovascular Department, Research Institute, Michael Reese Hospital

Evidence has accumulated that the thyroid gland must play an important role in the mechanisms responsible for the pathogenesis of atherosclerosis (Turner and associates, and Page) by virtue of the action of this gland on the blood cholesterol levels, on general metabolic reactions, and perhaps on other mechanisms at present not clearly understood.

In the Cardiovascular Laboratory of the Michael Reese Hospital, the general problem of atherosclerosis has been studied for the past several years, using the chick as an experimental animal. The chick is an omnivore, which spontaneously develops atherosclerosis between one-half and one and one-half years of age. The appearance of lesions can be accelerated by feeding cholesterol, and these closely resemble those seen in man.

Six groups of six-week-old White Leghorn chicks, each consisting of sixteen birds, were maintained on chick starter mash. Three groups received 2 per cent cholesterol in oil mixed in the mash, and the other three received 1 per cent cholesterol in oil. Analogous groups served as controls. Two groups received dessicated thyroid and two, potassium iodide (Table I). Blood cholesterol determinations were made (Brun method) at various periods during the experiment. Birds were autopsied after eleven and sixteen weeks, respectively, for all groups, and gross and microscopic examinations made of the aortas and thyroid glands.

All chickens in the control groups showed atherosclerosis of the aorta. A 2 per cent cholesterol diet did not result in significant differences between treated birds and controls. However, three of the treated birds were free of lesions.

TABLE I

PER CENT CHOLESTEROL IN DIET	THYROID MG./KG./DAY	POTASSIUM IODIDE MG./KG./DAY	DEGREE OF ATHEROMA OF AORTA. AVERAGE GROSS GRADING		ANIMALS FREE OF LESIONS
			THORACIC	ABDOMINAL	
2			2	1.0	0
2	50		2	1.3	0
	100–200		2.6	1.0	2
2		200	2.4	1.5	1
		800	2.3	1.5	0
1			2.4	1.2	0
1	100–400		1.7	0.1	0
	400–1000		0.9	0.5	1
1		800–2000	1.2	0.8	0

*Dazian Fellow.
†Deceased.

Reduction of the cholesterol in the diet to 1 per cent and increase of the doses of desiccated thyroid and potassium iodide resulted in significant differences. Chickens which received potassium iodide and especially those which received thyroid showed less numerous and less severe atheromatous lesions than control birds. Our results on chickens confirm those of Turner and others who worked with rabbits.

Discussion.—*Simms* raised the question whether other blood lipids parallel the cholesterol level. *Horlick* replied that phospholipids do; other fractions have not been studied. *Page* pointed out that all fractions of the blood lipids rise; in general, the neutral fat increasing most. This applies to both normal and hyperlipemic blood. *Simms* thought that differences in results of experiments of various investigators were partly due to the fact that they used animals of varying age.

Conclusion.—The mechanism of actions of thyroid needs further elucidation, as not even the reasons for the alterations of the cholesterol blood level in thyroid disturbances are known.

A STUDY OF RATE OF OXYGEN CONSUMPTION IN PATIENTS WITH ARTERIAL DEGENERATION AND A CONSIDERATION OF THE RELATION OF THE METABOLIC PROCESSES TO THE ONSET OF DEGENERATION*

MARGARET CHIEFFI, M.D., AND WILLIAM B. KOUNTZ, M.D., ST. LOUIS, MO.

From the Department of Gerontology, Washington University School of Medicine, St. Louis, Mo.

Studies have been carried out on the rate of oxygen consumption of patients suffering from varying degrees of arterial degeneration.

A group of 500 patients over 40 years of age were used and were studied for a long period. The metabolism of these older persons, as evidenced by the rate of oxygen consumption, was much more variable from individual to individual than is the case in subjects in the younger age groups. This variation, as far as we could determine, was not the result of thyroid dysfunction or other states which are commonly known to cause disturbances of metabolism. We found that the heat production in these patients varied from as low as 28 calories per square meter per hour to as high as 39 calories per square meter per hour. We divided our patients into three groups, according to the degree of arterial degeneration found in physical and radiologic examination. In the first group we placed those patients with evidence of early degeneration; in the second, those with moderate degeneration; and in the third, those with advanced arterial degeneration.

A study of the metabolic rates of the individuals in the different groups seemed to show that variations in the degree of degeneration were frequently associated with alteration in heat production. We found the lower oxygen consumption in those individuals in whom there was evidence of early degeneration. With progressing degenerative change, however, the oxygen consumption did not continue low, but tended to increase, and reached the highest figures in those patients with advanced disease.

From our studies it would appear that the metabolism in the aging individual passes through a cycle. The onset of degeneration is associated with a slowing down of the oxidative processes of the body. When degeneration has progressed to the point of causing breakdown of the organism, the metabolism is stimulated and the heat production rises.

Discussion.—These studies were based upon basal metabolism determination. *Stubbs* inquired about the correlation of blood lipids and basal metabolism rate

*Paper has been published in Geriatrics.

and *Morrison* about the relation of blood iodine to the basal metabolism. *Chieffi* answered that these factors were not studied and pointed out the technical difficulties of assays of iodine. *Wolffe* asked whether some patients were given thyroid only and others only stilbesterol and, further, whether the latter was given orally or parenterally. He stressed that not the height of the blood cholesterol but rather the saturation of blood with cholesterol is significant for the development of atheromatosis. He then discussed the literature concerning in vitro cholesterolysis. While *Morrison* remarked that this information fits into *Hueper's* concept of the genesis of atheromatosis, *Kountz* expressed his dissatisfaction with the cholesterolytic index as laboratory procedure.

Page stated that none of the work on the saturation of the blood with cholesterol, as far as he knew, has been confirmed. The height of the cholesterol level in the blood still remains the best index foreshadowing the occurrence of atherosclerosis.

Conclusion.—While nobody would admit it openly, dissatisfaction was felt that no better method of study of the metabolism in normal and abnormal aging is available than estimation of the basal metabolism rate.

FOURTH SCIENTIFIC SESSION

THERAPEUTIC CONSIDERATIONS IN THE STUDY OF ARTERIOSCLEROSIS

J. B. Wolffe, Philadelphia, Pa., Presiding

Round Table:

M. Bruger, New York, N. Y. (Moderator)

N. S. Davis, Chicago, Ill.
R. Holman, New Orleans, La.
A. G. Saidman, Washington, D. C.

General Discussion:

N. Barker, Rochester, Minn. (Leader)

J. T. Gault, Chicago, Ill.
L. N. Katz, Chicago, Ill.
W. Raab, Burlington, Vt.
J. G. Schlichter, Chicago, Ill.
M. M. Zuzman, Johannesburg, S. A.

THERAPEUTIC OUTLOOKS IN ATHEROMATOSIS*

O. J. Pollak, M.D., Wilmington, Del.

From the Wilmington General Hospital

Animal experiments contribute toward the treatment of human atheromatosis.

The therapeutic approach varies with the theory of development of atheromatosis one accepts. The importance of lipids, mainly of cholesterol and its esters, in this process has been generally acknowledged. There are many theories as to the mechanism of cholesterol deposits in the vessel wall: these again will guide the individual therapeutic efforts.

A study of the cholesterol metabolism reveals the various points at which one might try to influence it: dietary restrictions curtail the caloric intake and the ingestion of cholesterol. To some extent, the liver synthesizes cholesterol from other foodstuffs. Stimulation of hydrolysis of cholesterol esters may prevent their

*Paper not to be published in full at present.

absorption. Pancreatic extracts enhance the destruction of cholesterol in the liver; potassium iodide and other chemicals delay or prevent its deposit; and lipotropic substances such as choline remove liver fat. We do not know how to prevent cholesterol synthesis nor do we know how to influence esterification or to speed de-esterification in the liver. Good biliary drainage is important for elimination of cholesterol. Stimulation of the reticuloendothelial system may regulate cholesterol removal. Thyroid substance enhances the cholesterol metabolism.

Removal of cholesterol from the blood stream by oxygenation seems highly desirable. One must keep in mind that while marked hypercholesteremia exists in cholesterol-fed animals, the blood cholesterol level in patients with atheromatosis is hardly abnormal. Undue wear and tear of the vessels and physical and mental stress should be avoided. Mobilization of cholesterol from early deposits might be attempted through lipotropic action; calcification of arterial softenings might be forced.

Discussion.—This was a sketch of some aspects of the therapeutic problem. *Holman* thought that too much stress was given to cholesterol and that infection still plays a role in the etiology of atheromatosis. He wondered whether cholesterol esters are harmful, per se, because cholesterol deposits found in the body outside the circulatory system do not seem to do much harm. He felt that one generalizes too much in talking about "lipid substances." *Pollak* replied that it has been shown by Leary that inflammatory reactions are secondary to atheromatous lesions and also that cholesterol is a local irritant. Outside the vascular tree, cholesterol and its esters are commonly found in necrotic foci, frequently preceding calcification. *Schlichter* wanted more attention to be given to vasa vasorum as a causative factor, or factors, in the localization of atheromatosis. *Davis* denied that nicotine might be of etiological importance but agreed that it has to do with the symptoms of atherosclerosis. He thought it undesirable to speed calcification as a therapeutic measure. *Bruger* held dietary restrictions in hypercholestermia of essential xanthomatosis beneficial, but even large amount of lipotropic substances ineffective.

Conclusion.—There are numerous avenues open for therapeutic investigation on atheromatosis. Various phases of this disease are present simultaneously; therefore, prevention and therapy overlap. For the same reason, a multiple approach is essential.

CHOLESTEROL AND CHOLESTEROL ESTER LEVELS IN ACUTE MYOCARDIAL INFARCTION

LESTER M. MORRISON, M.D., LILLIAN HALL, M.D., AND ALBERT L. CHANEY, PH.D.
LOS ANGELES, CALIF.

From the Los Angeles County General Hospital

Over 200 consecutive patients under 60 years of age admitted to the Los Angeles County General Hospital because of acute myocardial infarction were studied within forty-eight hours after admission as to their cholesterol and cholesterol ester levels, and compared with a control group. In these studies comparative analyses were made also of the original Bloor-Knudson method of cholesterol determination, of the Sperry-Schoenheimer method, and of the new modification of the Sperry-Schoenheimer method. Their values are reported, indicating the errors inherent in the Lieberman-Burchard reaction. In 68 per cent, hypercholesterolemia was present.

In 48 per cent of 200 patients over 60 years of age with proved acute coronary thrombosis, hypercholesterolemia was found.

Discussion.—The cholesterol metabolism in coronary sclerosis was discussed. *Saidman* inquired about the sex distribution of patients with coronary lesions, and asked about the number of diabetic subjects in the series discussed and about vascular accidents. Among his own patients, women without diabetes never had coronary occlusions, while among diabetic subjects 27 per cent of all patients with occlusions were women. *Davis* stressed age differences beside those of sex. *L. Katz* wanted to know whether cholesterol assays were done during or 48 hours after infarction. A query of *Holman* was answered by *Morrison*; hypercholesteremia need not be present in wasting disease. He thought that urinary cholesterol estimation might replace its not wholly satisfactory determination in the blood.

The discussion then centered upon methods of cholesterol determination. *Bruger* pointed out that the relation between the amount of blood and Bloor's mixture influences the results of tests, and that Bloor's method in various modifications yields higher values than the technique of Sperry-Schoenheimer. *Holman* advocated uniformity of methods. Finally, *Pollak* asked for a small committee to investigate the various techniques and to recommend the most reliable method to the membership.

Conclusion.—The most important point of interest brought out by the presentation and discussion was the need for a standard method of cholesterol determination.

TEMPORAL ARTERITIS*

MAURICE PROTAS, M.D., AND AARON G. SAIDMAN, M.D.
WASHINGTON, D. C.

The thirty-four pathologically proven cases of temporal arteritis adequately described in the literature since the first report by Horton, Magath, and Brown in 1932 are critically reviewed and statistically tabulated.

The condition is found in members of the white race only. Women predominate over men by a ratio of two to one. The average age of the patients is 66.8 years. Temporal arteritis appears to be a specific disease characterized clinically by headache, loss of weight, painful mastication, fever, anemia, and leucocytosis. The typical pathologic findings consist of the presence of foreign-body giant cells in the media, in addition to other evidence of chronic arteritis. Autopsies indicating the presence of arteritis in vessels other than the temporals are reviewed. The headache appears to be due to the subcutaneous location of the temporal arteries.

The etiology is not definitely established, but it appears to be of infectious nature. Arteriosclerosis is believed to be a contributory factor. Despite some controversy, it is felt that the evidence indicates that temporal arteritis is similar to but different from rheumatic fever, thromboangiitis obliterans, and periarteritis nodosa. "Idiopathic Giant Cell Mesoarteritis" is therefore suggested as the more descriptive name for the disease.

Early recognition and biopsy seems to be the only method to prevent irreversible blindness which is becoming more frequently reported as a complication. Much has yet to be learned about the therapy of this condition. The newer antibiotics as well as the anticoagulants should be given a clinical trial. Periarterial infiltration with procaine is suggested.

A typical case is presented in which temporal arteritis was first suspected to be a complication of pernicious anemia.

Discussion.—This presentation stimulated a discussion on periarteritis nodosa in general by *Holman* and in relation to temporal arteritis in particular

*Paper is to be published in full length in the M. Ann. District of Columbia.

by *Bruger* and *Barker*. *Holman* found the sensitivity to sulfonamide of patients with temporal arteritis particularly impressive.

Conclusion.—Temporal arteritis appears to be a clinical entity rather than a pathologic one. The anatomic changes correspond to vascular diseases found independently of temporal arteritis.

DISSECTING AORTIC ANEURYSM: PATHOGENESIS AND SURGICAL SIGNIFICANCE*

ALEXANDER BLAIN, III, M.D., AND FRANCIS S. GERBASI, M.D.
DETROIT, MICH.

From the Department of Surgery, Alexander Blain Hospital, Detroit

The relationship of arteriosclerosis, hypertension, and other factors to the development of dissecting aneurysms of the aorta has not yet been solved. Modern textbooks of pathology and medicine lack unanimity in discussing the pathogenesis of dissecting aneurysm.

Dissecting aneurysms may occur in the absence of intimal rupture. Where no communication between the intramedial blood and the aortic lumen exists, it may be assumed that the source of the intramedial blood is ruptured vasa vasorum. It would seem logical, therefore, to consider the possibility that the intimal tears observed in so many dissecting aneurysms are secondary to the medial bleeding, rather than primary, and that the blood found in the dissection may arise initially from ruptured vasa vasorum, whether or not intraluminal blood eventually circulates through it. Two personally observed cases, in which there was no intimal rupture, and thirteen similar cases in the literature support the view that dissecting aneurysms are really intramedial hematomas. A recent case, diagnosed ante mortem, showed at autopsy two separate and distinct aortic dissecting aneurysms, each with its own intimal rupture. It may be tentatively concluded that dissecting aneurysms are due to some intrinsic lesion or lesions of the media rather than, for example, the bursting of a defective intima in a hypertensive patient with sudden increase of intra-aortic tension. The role played by the so-called idiopathic cystic medial necrosis of Erdheim in the predisposition to medial dissection is not clearly established.

The importance to surgeons of the diagnosis of dissecting aneurysms is emphasized. The protean clinical manifestations of dissecting aortic aneurysm may simulate nephrolithiasis, arterial embolism, acute pancreatitis, ruptured intra-abdominal viscus, and other surgical conditions.

Of 270 case reports studied, thirty-eight (14 per cent) were either diagnosed or strongly suspected as a surgical condition. In nine patients, operation was undertaken under the mistaken diagnosis of acute abdominal disease or other surgical conditions.

Discussion.—This paper was held by *Holman* to be a challenge to the accepted pathologic concept of dissecting aneurysm. *Schlichter* mentioned the occurrence of dissecting aneurysm in coarctation of the aorta. A possible reason for development of dissecting aneurysm is anoxemia of the wall of the aorta. *Saidman* advocated angiography as diagnostic aid. *Zuzman* stated that hypertension is rarely due to beriberi heart disease. *Raab* added that adrenal cortex hypertrophy is constantly encountered in vitamin deficiencies.

Conclusion.—It seems possible that dissecting aneurysm has its genesis in the media of the vessel wall. This is a type of vascular lesion where surgical therapy is more important than medical treatment.

*Paper is not to be published in full at present.

INTRAVENOUS ETHER: A NEW APPROACH TO THE THERAPY OF ARTERIOSCLEROSIS

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From the Clinical Medicine Research Laboratory and the Department of Metabolism, Touro Infirmary, New Orleans

In 1944, the discovery of the usefulness of intravenous diethylether in alleviating the ischemia and pain of diabetic arteriosclerosis obliterans was made. Further clinical trials were made at the Metabolic (Diabetic) Clinic of the Touro Infirmary of New Orleans. The results, after careful statistical evaluation, have been heartening; 80 per cent plus of the patients treated for impending ischemic gangrene and pain were saved from amputation.

Diethylether therapy has also given hopeful results in the treatment of patients with arteriosclerotic obliterans (nondiabetic), Raynaud's syndrome, Buerger's syndrome, and other angiospastic conditions.

Diethylether (2½ per cent) is introduced into a dilution media (1 liter) of 5 per cent glucose and distilled water. Both of the components are refrigerated to protect against possible explosive activity due to the high vapor pressure of ether.

Administration is governed by the physical condition of the patient. With no complications of cardiac origin, the ether solution may be administered in one and one-half hours; otherwise, a longer time may be necessary to protect the patient against shock.

The most promising single attribute of this treatment is its ability to cope with pain and impending necrosis. Actual arrest of the necrotic process has been seen, and reparative process has been noted. No untoward toxic effects of diethylether have been reported.

Discussion.—*Holman* felt that it is a "last resort" treatment after other measures have failed. *Saidman* and *Davis* inquired as to possible liver damage by ether. *Bruger* pointed out that during anesthesia there is a rise in blood cholesterol and lipids. The mechanism of this phenomenon might not be the same as that suggested by *R. Katz* but studies would be desirable. He wanted to know the duration of vasodilatation after administration of ether. *Gault* questioned the advisability of this type of treatment in obliterating arterial disease. *R. Katz* summarized by stating that ether acts upon collaterals. Sympathectomy should be performed in patients below the age of 50 years but not in older ones. Ether therapy fails in 20 per cent of patients and these should undergo surgery. On the other hand, where surgical treatment fails there still remains ether as a useful therapeutic weapon.

Conclusion.—While the method is worthy of much more penetrating investigation, it has not yet reached the stage of wide acceptance as a therapeutic procedure. The mechanism is completely unknown.

American Heart Association, Inc.

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ELECTION TO GOVERNING BODIES

At the meeting of the Board of Directors, held on March 11, 1948, Mr. Alfred C. Howell of Bethel, Conn., was elected to serve on the Executive Committee of the Board of Directors.

The following were elected to the Board of Directors and the Assembly:

Board of Directors

Dr. David D. Rutstein, Boston, Mass.
Mr. Don Francisco, New York, N. Y.
Mr. Emerson Foote, New York, N. Y.

Assembly

Mr. John H. Dunkin, Tulsa, Okla.
Mr. Maurice Goldblatt, Chicago, Ill.
Dr. John McEachern, Winnipeg, Manitoba, Canada
Dr. Robert M. Moore, Indianapolis, Ind.
Dr. Russell Pigford, Tulsa, Okla.
(Elected on Dec. 5, 1947)
Mr. Robert Z. Greene, New York, N. Y.
Mrs. Ruth P. McEldowney, Chicago, Ill.
Mr. Donald G. Price, New York, N. Y.
Dr. F. Janney Smith, Detroit, Mich.

TESTIMONIAL LUNCHEON HONORS RALPH EDWARDS AND THE PROCTER & GAMBLE COMPANY

Presentation of a check for over $1,500,000 was made to the American Heart Association by Ralph Edwards of the "Truth or Consequences" radio program at a testimonial luncheon held in Chicago on Wednesday, April 14. The check represented the total of public contributions made to the Association during the "Walking Man" contest.

The luncheon, arranged by members of the American Heart Association and presided over by Mr. S. DeWitt Clough, honored Mr. Edwards and the sponsor of the program, the Procter & Gamble Company, for their cooperation in the 1948 campaign to raise funds for the Association's continuing program of scientific research, education, and community service in cardiovascular disease.

Dr. A. R. Barnes, President, awarded to Ralph Edwards an illuminated scroll in album form signed by members of the Board of Directors of the Association.

Mr. Clough, who is a member of the Executive Committee of the Association, and Chairman of the Board, Abbott Laboratories, presented a large scroll to representatives of the Procter & Gamble Company. Speaking in behalf of the Association, he cited the company for its outstanding leadership in utilizing its radio resources to promote the public health.

Principal speaker of the luncheon which was attended by professional and lay members of the Association, as well as prominent representatives of business and industry, was Mr. Oscar R. Ewing, Federal Security Administrator.

PRELIMINARY CONFERENCE BETWEEN NATIONAL AND LOCAL ASSOCIATIONS

Representatives of local heart associations affiliated with the American Heart Association attended a preliminary conference in Atlantic City on May 2nd for discussion of basic relationships between the national and local associations. Representatives from forty-three additional cities interested in developing local heart associations were invited to this meeting.

The conference followed the action of the Board of Directors on March 11, 1948, which authorized the expenditure of funds for necessary full-time personnel to draft an outline of a proposal to formulate a policy and action program for the national association which will be submitted for consideration at the Annual Meeting in Chicago on June 18 and 19. The plan is to provide an outline of the long-term basic policies and objectives which could best be adopted by the Association, taking into account the relationship of the heart disease problem to the nation's public health program.

The plan will also suggest the organizational structure needed to attain these objectives; recommend steps to be taken with reference to agreements between the national and affiliated groups; methods by which the national association may encourage and assist the formation of new local associations; coordination with public agencies and with other voluntary agencies; development of methods for organizing programs in research, and professional and public education; and measures which the Association should encourage and assist local associations to undertake with respect to organizational structure, coordination with other community agencies, community services, and fund-raising.

NEW PUBLICATIONS

Two new pamphlets designed to increase the public's knowledge concerning general and specific phases of heart disease have been published in recent weeks. "Know Your Heart," a popular treatment of cardiovascular disease by Howard Blakeslee, science editor of the Associated Press, was prepared with the cooperation of the American Heart Association and issued by the Public Affairs Committee. "Employment and Heart Disease," by Dr. Leonard J. Goldwater, has been issued by the American Heart Association.

Copies of Mr. Blakeslee's pamphlet (No. 137) may be obtained at ten cents each from the American Heart Association, 1775 Broadway, New York 19, N. Y. It deals with the functioning of the heart, describes various aspects of heart disease, and outlines methods of treatment and prevention. The pamphlet also contains a series of typical questions asked by the public, with answers simply stated for the lay reader.

Dr. Goldwater's pamphlet consists of a series of questions and answers covering the employability of persons with heart disease. He cites the favorable experience reported in medical, trade, and governmental journals which demonstrates the advantages of hiring physically handicapped workers. Dr. Goldwater stresses the need for education of the public through the physicians of the community and by other means "to the fact that within reasonable limits and under medical supervision the majority of persons having heart disease may safely pursue useful occupations and otherwise lead fairly normal lives."

Copies of "Employment and Heart Disease" may be obtained from the American Heart Association.

PASSANO FOUNDATION AWARD

For the first time since the Passano Foundation was established in 1944, a dual award has been made. The cash award of $5,000 will be presented to Dr. Helen B. Taussig and Dr. Alfred Blalock, who developed the successful operative procedure for pulmonary stenosis. Presentation of the award will be made at the Palmer House in Chicago on the night of June 23 during the convention week of the American Medical Association.

The Passano Foundation was established by the Williams & Wilkins Company, medical publishers of Baltimore, to aid the advancement of medical research, especially research which bears promise of clinical application. Previous winners have been Dr. E. J. Cohn of Harvard for his work on fractionation of blood, Dr. Ernest Goodpasture of Vanderbilt for virus culture by the chick embryo method, and Dr. Selman Waksman of Rutgers for discovery of streptomycin.

Dr. Helen B. Taussig is Associate Professor of Pediatrics and Dr. Alfred Blalock is Professor of Surgery at the Johns Hopkins Medical School. Since the first "blue baby" operation was undertaken in November, 1944, more than 600 patients drawn from all parts of the world have been operated on at Johns Hopkins Hospital alone.

ANNUAL MEETING AND DINNER

The Annual Meeting and Twenty-First Scientific Session of the American Heart Association will be held in Chicago on June 18 and 19, 1948. The Stevens Hotel will be the headquarters for all meetings.

The Annual Dinner will take place on Saturday, June 19, 7:30 P.M., at the Palmer House. Members and wives, as well as those attending the Scientific Sessions, are invited to the Dinner. Official delegates of the Third Inter-American Congress of Cardiology will be guests of the American Heart Association.

Those planning to attend the Annual Dinner are requested to notify the American Heart Association as early as possible and to send their remittances in advance. The cost of the dinner will be $7.00 per person.

Mr. Thomas I. Parkinson, Chairman of the Board of Directors, will be the principal speaker of the evening. The Dinner will also mark the induction of Dr. Tinsley R. Harrison of Dallas, Texas, as President of the American Heart Association.